Die Tuberculose der Leber ist im Widerspruch zu den bisher gebräuchlichen Angaben eine der häufigsten secundären Tuberculosen nicht nur des kindlichen, sondern in gleicher Weise auch des erwachsenen Alters.
Nicht gar selten sind alle oder einzelne Tuberkel nur mikroskopisch sichtbar. Die Symptome der Lebertuberkeln werden so lange unbekannt sein, als die Diagnose der Leberkrankheiten überhaupt noch so schwierig ist wie bisher.

E. WAGNER (1861)

TUBERCULOSIS AND ASPIRATION LIVER BIOPSY

ITS CLINICAL SIGNIFICANCE IN DIAGNOSIS AND THERAPY

BY

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AND

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HAARLEM
DE ERVEN F. BOHN N.V.
1955

IN MEMORY OF
PROFESSOR W. A. KUENEN M.D.

FOREWORD

Aspiration liver biopsy can be considered as a justifiable procedure in patients suspected of liver disease — assuming that the right indications are present and the clotting mechanism has been thoroughly examined—but every proposal to extend the indications for biopsy has to be judged critically on its merits and on the value in diagnosis and treatment in each individual case in which one wants to apply the method The skill and the caution of the person who has to perform the biopsy counts in the assessment too It is fortunate therefore that my colleague Dr A J CH HAEX who is the originator of the problem that led to the publication of this monograph possesses both these qualities

The results of the investigations described in this monograph are so great that one may consider the biopsy wholly justified in the many difficult cases of tuberculosis where this so important diagnosis is in doubt provided that the pathological technique laid down by Miss C VAN BEEK is followed

For every older clinician who has had in the past some difficulty in imagining the mode of origin of haematogenous tuberculosis of organs in general this monograph will be a revelation Besides this we are shown clearly that an early and accurate diagnosis of doubtful tuberculosis of the lungs or any other organ as well as of the classic miliary tuberculosis has become readily attainable so that antibiotic treatment can be instituted as early as possible That this is for the benefit of many patients who have had to do without this treatment in a decisive stage of their illness because of the difficulty of early diagnosis goes without saying

J MULDER

ACKNOWLEDGMENT

With reference to the well-known fact that in sarcoidosis there are lesions in numerous organs (eyes, salivary glands, lungs, kidneys, bones) we set out in 1940, with the help of aspiration liver biopsy, to find out whether this disease causes such changes in the liver also. The tubercles which we found in nearly 100% of our cases greatly resembled those found in tuberculosis and we tried to ascertain whether there were any histological differences between the tubercles of tuberculosis and those of sarcoidosis, for this we performed aspiration liver biopsy in patients with tuberculosis. We owe a great debt to the late Prof. KUENEN, University Hospital, Leiden, for the fact that he agreed to do these investigations in his clinic at a time when the clinical development of the liver biopsy had hardly begun.

During the war the investigations had to be discontinued, but after the war — Prof. KUENEN having retired in the meanwhile — they were resumed with the full co-operation of his successor, Prof. MULDER. For his co-operation we wish to express our thanks to him here.

Thanks to the scrupulous care with which our technician, Miss A. SMIT, made the serial sections, it was possible for us to do serial examination in all our cases. Without these it would have been difficult, not to say impossible, to find the smaller lesions of types III and IV, and the diagnosis of tuberculosis would have been missed many times. For the devotion with which she performed her share in our work we want to render thanks to Miss SMIT.

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For the financial help we express our thanks to the Board of the 'Jan Dekker Fonds'

We owe gratitude to Mr P A Bouter who made the photomicrographs

In conclusion we want to express our thanks to Dr Bernard Lennox of the Postgraduate Medical School of London for his assistance with the translation of this monograph

CONTENTS

PREFACE

In spite of the multiplication of modern methods of clinical investigation in liver disease, especially the numerous liver function tests, we are forced to admit that in many cases diagnosis is still by no means easy. During the past fifty years, therefore, the need has been increasingly felt for a simple, harmless, and reliable aspiration biopsy method. Exploratory liver puncture has been performed for more than a century (particularly in tropical countries) in order to make a diagnosis in cases of abscess and cyst; the earliest report we have been able to find was that of STANLEY in 1833. For histopathological examination of the liver, however, recourse was nearly always made to laparotomy with formal surgical removal of a wedge biopsy from the liver margin. For the patient such an operation entails both discomfort and some degree of risk; from the pathologist's point of view it suffers also the disadvantage that the margin of the liver, with its excess of connective tissue, is often a misleading sample.[1]

The size of the liver and its position in the right hypochondrium render it easily accessible to needle biopsy. Moreover, in most cases in which we are likely to be interested the liver lesion is a diffuse one or, if it consists of discrete foci, such foci are diffusely distributed, so that a small biopsy, especially when it is examined in serial section, may very often suffice to give a completely adequate picture of the state of the entire liver. It is only in the presence of focal morbid conditions such as, for instance, localized tumours, that needle biopsy is not suitable, in that we are more or less dependent on chance for obtaining an adequate sample in such cases.

The first mention of aspiration liver biopsy was that of von FRERICHS, whose assistant PAUL EHRLICH used this technique to study the glycogen content of the liver in diabetes mellitus (1884)

Good results were obtained by SCHUPFER (1907), BINGEL (1923) and OLIVET (1926), but owing to the risks attached to their technique it failed to acquire any general popularity Thanks to the work of IVERSEN and ROHOLM (1939) we have now a satisfactory and safe method, one which we ourselves have used on approximately 2000 occasions without a single serious complication

Some pathologists are rather sceptical of the diagnostic possibilities of a small column of liver tissue, $1\frac{1}{2}$ to 3 cm long, and 1 to $1\frac{1}{2}$ mm in diameter In our opinion, however, these possibilities are very great, exceeding those of marginal biopsy in laparotomy, and, *paradoxical as it may seem, have advantages* even over the larger pieces of tissue obtained at autopsy On account of the small size of an aspiration biopsy all the details may be examined with a minuteness seldom possible in studying the larger pieces examined at autopsy When moreover the little column of *aspirated tissue is examined in serial section,* one learns to know the normal and the pathological patterns of the liver in a manner impossible in autopsy tissues, unless the needle technique is applied in them also, for serial examination of a relatively large portion of the liver, such as is ordinarily used *for postmortem histology, is so exacting that* one loses one's way in the liver pattern

Apart from the diagnostic (and therefore therapeutic) possibilities of the method in studying liver diseases, the aspiration biopsy offers similar advantages in other diseases (HODGKIN's *disease, sarcoidosis, tuberculosis, berylliosis, etc*) From a more general standpoint the aspiration liver biopsy is also very valuable At autopsy one learns to know only the final stages of disease, biopsy, on the other hand, gives a dynamic character to histopathology, so that the pathogenesis of many diseases is *illuminated* It should also be remembered that postmortem histology is considerably disturbed by the autolytic changes to which the liver is so liable

Needle biopsy of the liver only serves a *useful purpose* if full cooperation on the part of the pathologist can be assured.

The physician must have a perfect knowledge of the technique the indications and the contra-indications but the pathologist must also be aware of the high demands that will be made upon him He must be expert in the pathology of the liver and he must be prepared for the laborious examination of serial sections which greatly increases the value of the method and is in some cases indispensable Finally one must also be able to rely on the meticulous assistance of a skilled technician

In this monograph we are concerned with the use of the aspiration liver biopsy in the early diagnosis the therapy and the prognosis of the different forms of tuberculosis It is especially in these cases that serial sections are important and as their examination may take up a great deal of time one might be inclined to question the economics of the method In the analogous situation of the examination of bronchial secretions for tumour cells WOOLNER and McDONALD describe a workable procedure The slides are examined systematically by trained technicians and the suspicious areas marked for verification by the pathologist The same working method may be followed in the detection of tubercles in liver biopsies

Needle biopsy is only justifiable if the abovementioned conditions are adequately fulfilled but when that is so the results are so spectacular that the little group of workers concerned count all their pains well spent

CHAPTER I

TECHNIQUE AND CONTRA-INDICATIONS

Before discussing the diagnostic value of aspiration liver biopsy in the various forms of tuberculosis, we think it proper to give a summary of our method and to discuss the contra-indications which we consider important

TECHNIQUE (AFTER IVERSEN AND ROHOLM)
Aspiration biopsy of the liver is performed with a dry sterilized needle of V2A steel, 18 cm long and with a diameter of 1.4—1 6 mm with sharp serrations at the end, and provided with a trocar and a dry-sterilized 10 ml syringe with a stopcock

The exact site for the liver biopsy is carefully established For anatomical reasons, puncture is performed in the *posterior axillary line* (personally we prefer a slightly more dorsal location) a little below the margin of the diaphragm and the lung, and *never below* the 9th intercostal space In exceptional cases puncture of very large livers may be performed at a slightly lower point but this should be done for very special reasons only If the puncture is made in the 8th or 9th intercostal space and slightly dorsal to the posterior axillary line, there will be no risk of fatal injury to vital parts and in this respect there could be no better place for the operation

Puncture is performed with the patient sitting or lying, in the latter case preferably with the patient lying on his left side We prefer the sitting position, others (IVERSEN and ROHOLM) the lateral recumbent position on the left side It is desirable to have an X-ray of the thorax and the hepatic region prior to the operation as it has become evident that subnormal convexity of the diaphragm may be responsible for failure of the

puncture Interposition of an intestinal loop which has not been identified may have most unpleasant consequences but we never saw any complications of this type after accurate percussion At the slightest sign of tympanism in the hepatic region we make an X-ray examination, which is often extended to the colon

When the exact site has been located, the skin is thoroughly cleared, first with alcohol and then with iodine The skin and underlying tissues are then anaesthetized, after this the needle track (up to and including the diaphragm and peritoneum) is anaesthetized, particularly during deep expiration With adequate practice, the anaesthesis can be made efficient enough to eliminate pain almost completely from the operation The crucial point is the diaphragmatic pleura If a thick trocar is used, incomplete anaesthesia of this structure may give rise to violent pains in the epigastrium, often radiating to the shoulders, which may cause shock A 2 per cent novocaine solution is used as an anaesthetic We have discontinued the combination of novocaine and adrenalin, as this sometimes resulted in a slight collapse Such a collapse, though not serious in itself, necessitated postponement of the biopsy Part of the novocaine may enter the blood stream, and also cause a minor collapse

When the anaesthetic has been injected, the patient must be trained to make a deep expiration and then refrain from breathing for about 10 seconds. At the previously determined spot the skin and fasciae are pierced by a vaccination stylet, and the liver needle with trocar in place is then inserted If then it is found that the local anaesthetic is adequate, the liver needle now penetrates through the pleural sinus into the diaphragm, this can easily be observed, as the trocar follows the respiratory movements The patient is now requested to stop breathing for 10 seconds, and fix his chest in the position of deep expiration, in which, for obvious reasons, liver biopsy is most easily performed Next the needle pierces the diaphragm, the trocar is withdrawn and the 10 ml syringe with stopcock is attached to the needle A vacuum is then produced by withdrawing the piston of the syringe as far as possible The needle is now introduced into the

liver for a few centimetres a rotary movement round its long axis being given to it as it advances This action punches out a small piece of liver tissue The needle is then quickly withdrawn from the liver care being taken that the syringe remains firmly connected as otherwise the operation will definitely fail Atmospheric pressure now pushes the piece of liver tissue into the *vacuum of the syringe Sometimes the fragment of tissue lodges* in the needle this should be born in mind if a failure is suspected As a rule the liver tissue is fixed in a 4 per cent solution of formaldehyde and processed like other biopsy material

GILLMAN and GILLMAN have developed a promising technique the needle and the syringe are permanently attached to each other the trocar in the needle is fixed to the piston which therefore withdraws the trocar along with it when a vacuum is produced This materially reduces the time needed for the operation *

At each puncture we should consider the need for a culture of pathogens (B coli tubercle bacilli etc) from the liver tissue and for a smear to be stained by GIEMSA s method which may be used together with the blood smear

Reactions We must now consider the possible reactions which may follow puncture These are generally slight some patients do not feel anything at all If necessary we even perform puncture on out patients who return home after a few hours rest

Possible reactions are

1 Epigastric pain with possible radiation to the shoulders (usually the right) originating from the diaphragmic pleura This pain usually subsides rapidly

2 After biopsy some patients have pain on breathing for some hours after the effect of the anaesthesia has ceased In such cases it is advisable to give a subcutaneous injection of 20 mg of pantopon

3 Sometimes there is a slight rise of temperature for a short period If this should last it may indicate a complication resulting e g from a non-sterile needle or a liver infection We have seen one such case only in our own series (liver infection)

* See Bibliography GILLMAN and GILLMAN ([illegible])

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* (see bibliography GILLMAN and GILLMAN HAEX)

4 Occasionally we have observed slight shock of short duration, never severe shock necessitating a blood or plasma transfusion

5 Very rarely we have seen a temporary paralytic ileus We have not established the cause of this, but we believe it arises from irritation of the peritoneum or perhaps a slight haemorrhage in the abdomen

6 Thrice we observed a slight pneumothorax which did not affect the patient at all

Complications Is there any risk attached to liver biopsy? This question must be answered in the affirmative Injudicious use of the needle or an incorrect indication may cause serious complications, which may even be fatal

These complications may be

1 Haemorrhage, which may be prevented in most cases We have never seen a severe haemorrhage On one occasion we observed at laparotomy some blood in the abdominal cavity of a patient who had been punctured some days before the operation, but had not shown any severe reaction In order to prevent unexpected copious haemorrhages it is essential to examine the clotting mechanism in every patient, as discussed below under contra-indications

2 False route (technical failure)
3 *Infection* (*incorrect indication* or non-sterile needle)
} Not real complications

Failure of the operation may be due to

1 Insufficient convexity of the diaphragm
2 Imperfect or non-airtight attachment of the syringe to the needle
3 Right pleural effusion or ascites
4 Poor condition of instruments (leaking syringe, blunt needle)
5 Patient s collapse following anaesthesia

CONTRA-INDICATIONS

Aspiration biopsy of the liver, if practised without sufficient knowledge of contra-indications, constitutes a serious threat to the

patient s life The following is a summary of these contra-indications

1 *Hæmorrhagic tendency* In order to establish the condition of the patient s clotting mechanism it is necessary to determine the bleeding clotting and prothrombin times of the blood Our routine preliminary examination includes also determination of clot retraction and thrombocyte count Persistent deviations from normal in any of the above figures contra-indicate biopsy This restriction often prevents biopsy in a case in which it appears to be indispensable to establish a diagnosis Nevertheless the temptation to attempt puncture under these circumstances should be resisted In case of doubt it is better to postpone the operation and make a final decision later In any event jaundiced patients should be given vitamin K two or three days before the operation. On no account should it be performed until the prothrombin time has become normal

2 *Cholangitis* Biopsy is dangerous in cases of jaundice with fever accompanied by the presence of B coli or other pathogens in the duodenal fluid (when as a matter of fact gallstones are usually present) Even a slight haemorrhage caused by puncture may carry infected matter (blood or bile) from the liver into the abdominal cavity and cause serious peritoneal reactions a subphrenic abscess or even diffuse peritonitis In such cases therefore examination of the duodenal fluid is necessary in order to identify a possible inflammation of the intrahepatic biliary ducts (cholangiolitis) It will often be necessary to forego histological examination of the liver for this reason in cases where it would have been very valuable The liver of a patient suffering from obstructive jaundice due to carcinoma may be infected consequently great caution should be exercised in performing biopsy on such patients

3 Liver puncture is inadvisable when the patient is suffering from an *intercurrent infection* An existing bacteriaemia might infect the haematoma of the puncture thus causing a subphrenic abscess

4 An *asthenic build* necessitates greater caution among other

reasons because puncture is made more difficult by the visceroptosis which is so often found with this type of physique

5 Like IVERSEN and ROHOLM, we consider *right-sided pleurisy* a contra-indication — a matter which needs no further anatomical argument

6 Puncture should not be performed on patients suffering from a *local skin infection* (risk of infection)

7 As some patients are prone to increased haemorrhage during *menstruation*, puncture should not be performed during the periods

8 A possible *anomalous position of viscera* (situs inversus) should be taken into account Particular attention should be paid to interposition of the colon, which may be ascertained by careful percussion or X-ray examination before the operation

9 With *children* it is, of course, generally inadvisable to attempt puncture they cannot hold their breath Exceptions might be made for very large livers (see bibliography VAN BEEK and HAEX)

10 It goes without saying that a puncture is inadvisable when the patient is suffering from a *coronary arteriosclerosis*

11 Puncture should not be performed on patients suffering from *amyloidosis*,

12 That *lack of cooperation* on the part of the patient is a contra-indication goes without saying

The general rule is

No puncture should be performed on any patient on whom a laparotomy would be deemed inadvisable !!

CHAPTER II

INTRODUCTION

We propose to discuss first the value of aspiration biopsy of th liver with regard to the diagnosis, the therapy and the prognosis of tuberculosis before going on to sketch the value of aspiration liver biopsy in relation to the pathogenesis of tuberculosis.

The fragment of liver tissue obtainable by needle biopsy, minute though it is, is sufficient to influence fundamentally the clinical practice of tuberculosis. In the course of time pathology has gradually developed from a static science based on the autopsy into a more dynamic branch of medicine. By means of biopsies we are now learning the histopathological substrate of various clinical pictures in all their stages. Aspiration liver biopsy in particular has proved to be a most valuable aid in the diagnosis of numerous diseases; we shall exemplify this in the case of tuberculosis by means of extensive investigations.

The starting-point was an observation made in 1941 that in practically all cases of sarcoidosis tubercles and small epithelioid cell granulomata could be found in the liver biopsy. This made examination of serial sections indispensable. In order to find out whether there were any histological differences between the tubercles of sarcoidosis and those of tuberculosis we performed liver biopsies in 1946 on fifteen patients in whom the diagnosis of tuberculosis had been established bacteriologically — almost all being cases of pulmonary tuberculosis and none having clinical miliary tuberculosis. On cutting serial sections of the liver fragments from these 15 cases we found tubercles in fourteen. In addition to the well-known caseating and epithelioid-cell tubercles and conglomerate tubercles in the portal

spaces, we observed, just as in sarcoidosis, *minute epithelioid-cell* granulomata in the parenchyma In early 1947 the serial-section examination of forty liver biopsies in sarcoidosis and forty biopsies in tuberculosis showed that it was impossible to establish clear histopathological differences between the two clinical pictures — *except, that is, for caseation,* which we never observed in sarcoidosis (there are, however, a few reports in the literature of necrosis in this disease)

These investigations led us to enlist the liver biopsy as an aid in the early diagnosis of tuberculosis When streptomycin and P.A S made their appearance the whole picture of the therapy and prognosis of the disease was altered To the diagnostic indication for liver biopsy now the therapeutic-prognostic one was added, for modifications in the clinical picture due to modern antibiotic and tuberculostatic treatment could be elucidated when liver biopsies were performed every two or three months Since 1947 some results have been published

It has seemed to us desirable to classify the tubercles that were found more carefully than is usually done Without the examination of serial sections it is impossible to acquire a full picture of the exact location, the size, the presence or absence of caseation or fibrinous exudation, the type of cellular exudation, the presence and the type of the giant cells, and the age of the lesion The number of foci and their localization size, character, and age are ascertained not only for scientific reasons, but also for practical clinical purposes All this is set out in what we have called the *tuberculogram* of the liver (see table III)

Over one hundred sections of each liver biopsy were examined Among the advantages of this method of examination was the *frequent demonstration that tubercles* which seemed to lie in the parenchyma could be proved several sections later to be attached to a portal space *Caseation was only occasionally* observed, unless the case was one of miliary tuberculosis When caseation was present, it was nearly always possible (though sometimes only *after a prolonged search in many sections*) to demonstrate some acid-fast rods, sometimes in the caseous mate-

rial, but more often phagocytosed by the giant cells outside it. As we found that staining according to HALLBERG yielded better results than the ZIEHL-NEELSEN technique, we used only the former method On only a few occasions was it possible to demonstrate acid-fast rods in non-caseating epithelioid-cell tubercles

With regard to the giant cells, too, serial examination proved very instructive In 1868 LANGHANS called attention to the peripheral distribution of the nuclei, which are found sometimes in the form of a circle, but sometimes in polar groups Serial examination showed us the giant cells in three dimensions, which sometimes yielded surprising results At present we will only say that the giant cell type afterwards called after LANGHANS, with the nuclei in the form of a circle or a horseshoe, is by no means always present or predominant We often came across giant cells (also described by LANGHANS in tuberculosis) of the foreign body type and the benign giant-cell tumour type The cytoplasm is often large and vacuolated, dozens of nuclei being seen together We observed neither mitotic figures in the giant cells, nor SCHAUMANN's corpuscles On one occasion a giant cell was seen to contain a so-called 'asteroid body." Our investigations did not yield any suggestions regarding the origin of the giant cells we are unable to say whether they result from repeated mitosis without cell division or from fusion of many epithelioid cells

As for the cells of the connective tissue, no fresh points of view emerge According to the age of the lesion epithelioid cells (occasionally dividing), fibroblasts, young and old fibrocytes, and finally scar tissue with or without hyalinisation were seen We gained the impression that it is especially the caseous tubercle which becomes transformed into the so-called hyaline ball

Special attention was devoted to the cellular exudate Young tubercles, built up of epithelioid cells contain lymphocytes, side by side with neutrophils and or eosinophils, and sometimes plasma cells Older tubercles contain only lymphocytes The age of the tubercle can be estimated from the elements of the

connective tissue, the presence of mitoses, and the type of the cellular exudate present

Finally we wish to call attention to several points which the serial sections taught us regarding the size of the tubercles First of all we must point out that the word "miliary" is often used in a wrong sense It really means "the size of a millet seed" (i e 2—3 mm), and therefore a miliary tubercle must be easily visible to the naked eye Microscopically, such lesions mostly prove to be conglomerate tubercles Autopsy experience shows that true miliary tubercles are not often seen in the liver, submiliary tubercles, on the other hand occur very frequently As the standard liver biopsy has a diameter of about 1 5 mm, it is clear that only part of any miliary tubercle could be present in the biopsy, never a complete lesion So far we have not seen a single example We must, of course, allow for the possibility that the needle slips past a lesion of this size As most tubercles in the liver are of submiliary size it is this type that is found in the liver biopsy We have subdivided these tubercles into five types, viz O, I, II III, and IV this classification is based on the greatest diameter observed in the series (see Table I and photomicrographs) The largest are macroscopically almost the size of a pin's head, and as they are extremely rarely seen in the liver biopsy we have ranged them under the type O Microscopically they are mostly, but not always conglomerate tubercles They are situated in the portal spaces, and may have caseous centres Of the submiliary tubercles of types O, I and II type I and especially type II are the ones which occur most frequently in the liver in cases of tuberculosis, irrespective of the location of this disease in the body They are nearly always found in the portal spaces The skilled observer can just observe them with the naked eye as minute grayish-white points They often contain giant cells and are sometimes caseous Like type O they form scars and may become hyaline balls When such a hyaline ball is examined in serial sections a giant cell may suddenly emerge and also a solitary lymphocyte

The smaller types III and IV are only visible under the micro-

scope They occur in the parenchyma as clearly outlined epithelioid cell granulomata of round to oval shape they very rarely contain a giant cell Most often they are situated near the centre of the liver lobule occasionally attached to the wall of the central vein more often to a hyperaemic capillary They never caseate The epithelioid cells do not become ordinary fibrocytes their nucleus which is at first vesicular and palestaining becomes in

They will be considered in greater detail in Chapter XVIII Meanwhile Table I summarizes the character of the five types of tubercles

Lesions of types III and IV differ in several aspects besides their small size from classical tubercles and we propose in what follows to refer to them as *subtubercles* using the word *tubercle* as a general term for the whole series and *submiliary tubercle* to refer especially to lesions of types O I and II We introduce this new term subtubercle with considerable trepidation but it seems to us a great advantage to mark in this way their difference from the generally recognized larger lesions

Although nearly a century ago several pathologists (WAGNER 1861 VIRCHOW 1863 ORTH 1876 ARNOLD 1880 SIMMONDS 1880) examined microscopically the organs of persons who had died of generalized miliary tuberculosis or cavitating tuberculosis of the lung and recorded the fact that submiliary tubercles occurred frequently in the liver until a short time ago tuberculosis of the liver was looked upon as being clinically of no importance (B FISCHER GRUBER and BOYD) Since 1946 this view has been abandoned in our department

We shall now pass to a systematic discussion of the indications for aspiration liver biopsy in the various forms of tuberculosis This will be followed by a discussion of the results of our investigations after which this monograph ends with a table of the tuberculograms made from the liver biopsies which have been discussed and a series of photomicrographs

conjunctivitis which however, soon disappeared After rather more than a year recovery was complete and now, 4 years later she is in good health.

Case II Miss v d E, aged 20, had been ill for a fortnight Her family physician reported that the tuberculin tests were negative Ten days later the test of VON PIRQUET proved to be strongly positive

The physical examination did not reveal any abnormalities The temperature was subfebrile The erythrocyte sedimentation rate was 32 mm during the first hour, and 64 mm during the second hour The blood picture revealed slight toxic alterations The roentgenogram of the chest showed in the right middle zone a round indistinctly bordered shadow and an enlarged right hilus

of

sections) 68 sections were stained with haematoxylin-eosin 70 sections were stained according to HALLBERG but no acid-fast rods were found Among the sections stained with haematoxylin-eosin 30 foci in total were observed of which 28 lay in the parenchyma and 2 in the portal tracts 21 foci belonged to type II 7 to type III and 2 to type IV All were young epithelioid-cell lesions with marked cellular hyperplasia Several foci were very vaguely outlined against the parenchyma In total 3 giant cells were seen There was no necrosis or fibrinous exudate There were no neutrophils but besides lymphocytes several eosinophil leucocytes were observed *Conclusion* Extensive recent haematogenous dissemination

In consequence of these findings the patient was advised to undergo a strict rest-cure in a sanatorium Before going there she was subjected to a careful examination of the chest on which occasion a slight improvement was found She appeared to recover completely after a strict rest-cure of three years duration but $2^1/_2$ years later a new pulmonary lesion developed Surgery is at present being considered

What is the indication for liver biopsy in this type of tuberculosis? In the first place the cause of the irregularity observed on the X-ray picture of the chest may be ascertained with great promptitude in some cases at least At present we have not sufficient experience on this subject but we are of the opinion that there are adequate grounds to expect that this particular

form of tuberculosis will not be an exception to the rule that every active tuberculous focus is prone to produce a haematogenous dissemination, and that this may be detected by means of aspiration biopsy of the liver if the aspirated material is cut in serial section

For theoretical reasons also one might expect a haematogenous dissemination of tubercle bacteria from a primary infection this will be especially clear from the fact that in these cases there is no question as yet of any *immunity, so that the tubercle* bacteria can develop freely It goes without saying that immunity factors play an important (if not decisive) part during the first contact with the tubercle bacilli

Both cases examined in this group have been positive, and though they number only two this would seem to give a substantial amount of support to the above views

We need hardly say that in these patients the indications for aspiration liver biopsy do not often arise unless the scientific inquiry is regarded as the main object In spite of this, however, there may be occasions when time presses and it is not possible to await the results of the culture of the sputum or the stomach washings From the nature of things this form of tuberculosis is mostly observed in children, and therefore for accurate diagnosis of an infiltration in the lungs one often has to rely entirely on the clinical and roentgenological findings Generally speaking we consider it unwise to perform aspiration liver biopsy by the IVERSEN and ROHOLM technique in children * This objection does not hold good in the case of adults, it is especially in their case that this diagnostic method will be often resorted to, as the differential diagnosis of an infiltration in the lung sometimes causes great difficulties Further, it is possible in these cases to establish the presence of a haematogenous dissemination objectively by means of aspiration liver biopsy This is of paramount

* We have as yet no personal experience with the GILLMAN BRYDEN needle in children The GILLMAN brothers (personal communication 1954) have performed many liver biopsies in children with this needle (constructed for them by BRYDEN) without a single mishap (see page 7)

importance, for it is the fresh disseminations that are especi sensitive to modern therapeutic agents Later on we shall rev to this in greater detail

As in many forms of tuberculosis it is possible in these ca to imagine that small foci, similar to those in the liver tiss may be found elsewhere in the body, for instance in the mening It is, however, in practice impossible to perform lumbar pu ture regularly in all these patients Later on we shall ment the considerations which have led us to introduce repea examination of the C S F in a select group of patients (LANDOUZY's typhobacillosis and miliary tuberculosis)

In the third place, aspiration liver biopsy enables us to obse the degree of the activity of the process, and it is clear t generally speaking fresh tubercles are found in these cases V would point out once more however that our range of ex rience is as yet inadequate to give a final opinion on the activ of these forms of tuberculosis The question of any alterati which may occur in the histological appearances in liver bio at the time of conversion of the tuberculin reaction from ne tive to positive, and the effect of inoculation with B C G, fascinating subjects for future studies

we subjected these patients to a number of successive punctures

CASE HISTORIES

Case III Mr W, 912/1948, aged 18, had been ill for about six months with periods of high fever On physical examination no irregularities were found, apart from a doubtfully palpable spleen The erythrocyte sedimentation rate was 56 mm during the first hour, and 85 mm during the second h[illegible] -
malities [illegible] is
for typh[illegible] e
tuberculin test (VON PIRQUET) was positive

Gradually a fairly distinct shadow became visible on the X-ray of the chest It lay next to the hilar vessels, rendering the diagnosis of tuberculosis of the hilar lymph glands probable To settle the matter the patient was transferred to our clinic for an aspiration liver biopsy The pathological report on the liver tissue read as follows

"The biopsy measured 2 8 cm long, and was examined in serial sections (108 sections) 66 sections were stained with haematoxylin-eosin, and 42 were stained according to HALLBERG No acid-fast rods were observed

In the 66 sections stained in the usual fashion 76 tubercles were found Only 4 of them are portal, the other 72 being situated in the parenchyma Two foci are of type I, 9 of type II 36 of type III, and 29 of type IV Out of the 76 foci 39 are recent, 28 of the intermediate type, and 9 must be called old This leads us to suspect the occurrence of several episodes of dissemination The two tubercles of type I (situated in the portal tracts) contain giant cells and a trace of fibrin Necrosis is nowhere to be observed Several neutrophil leucocytes and only one eosinophil leucocyte were found in the fresh tubercles *Conclusion* multiple partly recent, partly older submiliary tubercles and epithelioid-cell subtubercles, practically all of them localized in the parenchyma It is most probable that haematogenous dissemination took place on several separate occasions"

The patient was treated with streptomycin and promin combined with good nutrition and strict bed-rest Some time after the liver biopsy was performed the stomach washings proved to contain tubercle bacilli on culture One week after the commencement of anti-bacterial treatment the temperature had fallen to normal values The disease subsided gradually and this was confirmed by a second and a third biopsy, done respectively about the middle and at the end of the streptomycin treatment

The pathological report on the second liver biopsy, which was performed nearly two months after the first one, read as follows

"The biopsy measured 1 2 cm long, and was examined in serial section (108 sections) In total 34 foci were found, 33 of them being in the parenchyma, and one portal Four foci are of type II, 19 of type III, and 11 of type IV. Out of the 34 there are 4 of a recent type, 18 of an intermediate type, and 12 are old (the latter include 3 scars) No necrosis or fibrinous exudation was observed There are no giant cells Eosinophil leucocytes are not observed, but an occasional neutrophil leucocyte is seen A sporadic fatty vacuole can be seen in the parenchyma

Conclusion multiple, submiliary foci in the parenchyma, showing a shift towards an older type as compared with the previous biopsy."

The pathological report on the third biopsy, which was performed two months after the second, and four months after the first, read as follows·

"The biopsy measured 1 8 cm long, and was examined in serial section (122 sections) 29 subtubercles were found, 28 of them being in the parenchyma, and one in a portal tract Out of these, 13 are of type III, and 16 of type IV Four of them are scars, viz one of type IV, and three of type III 13 foci are relatively recent Apart from an occasional fatty vacuole and a trace of periportal nuclear glycogen we observed no abnormalities

Conclusion Multiple subtubercles in the parenchyma, showing a shift towards a somewhat older type, as compared with the two previous biopsies However, the haematogenous dissemination has not yet come to a standstill"

After the streptomycin treatment had been completed the patient was discharged in a good condition At home he had to continue the rest cure, combined with good nutrition and extra vitamins The most recent follow-up examination (5 years after discharge from hospital) revealed nothing of note from a clinical point of view He is in excellent condition and has resumed work

Case IV Mr K , 1372/1948, aged 17, became acutely ill three weeks before his admission (temperature 38 4° C , shivering, malaise) He also complained of night sweats and headache On admission he had a high fever On physical examination we did not find anything of note except palpable lymph nodes at the angles of the jaws and in the neck, and a palpable spleen The erythrocyte sedimentation rate was 52 mm during the first hour, and 82 mm during the second hour The blood picture showed a slight anaemia (Hb 70 %) and slight toxic changes in the leucocytes No

abnormalities were found in the urine The tuberculin test (VON PIRQUET) was positive The X-ray picture of the lungs showed an enlargement of the left hilus on tomographic examination, however, it was not possible to demonstrate a definite glandular swelling

After the exclusion of other causes that might have been responsible for the clinical picture (the agglutination reactions to typhoid, paratyphoid, and brucellosis were negative, the urine was sterile and the blood culture was also sterile), we decided in order to establish the diagnosis to perform an aspiration liver biopsy The pathological report on the liver tissue read as follows

> "The biopsy measured 3 4 cm long, and was examined in serial section (120 sections) 108 sections were stained with haematoxylin-eosin, 12 sections by HALLBERG's method There is a striking hyperaemia In total 12 foci were observed, all of them being of a recent type
>
> [illegible]
>
> lymphocytes and many neutrophils, besides one acid-fast rod Out of the other 11 foci 5 are of type III and 6 of type IV Several portal tracts contain neutrophils and eosinophils The parenchyma contains a normal quantity of glycogen
>
> *Conclusion* acute haematogenous tuberculosis"

Now that the diagnosis of tuberculosis had been established it was decided to treat the patient with streptomycin and promin After seven days his temperature had already fallen considerably Acid-fast rods had meanwhile been found in the patient s sputum but cultures for tubercle bacilli proved negative Tubercle bacilli were never demonstrated by means of any culture technique in this case

After two months the temperature was still subfebrile, and it was decided to perform a second liver biopsy The pathological report of the tissue read as follows

> "The biopsy measured 3 1 cm long and was examined in serial section (112 sections) There are now no fewer than 64 foci of a rather young large-cellular type but distinctly older than eight weeks ago No necrosis or fibrin is seen anywhere and there are no eosinophil leucocytes and only occasional neutrophil leucocytes There are a few giant cells of the LANGHANS type Out of the 64 foci 21 are localized in the portal spaces and 43 in the parenchyma 13 belong to type II, 34 to type III and 17 to type IV
>
> *Conclusion* extensive haematogenous dissemination"

Therapy with streptomycin promin, and P A S which was added after six weeks was therefore continued After three months the temperature

was still subfebrile but the erythrocyte sedimentation rate had fallen to 9 mm during the first hour and 24 mm during the second hour Streptomycin treatment was then stopped, and therapy continued with P A S and promin A third biopsy was performed two months after the second The pathological report on the liver tissue read as follows

> 'The biopsy measured 2 7 cm long and was examined in serial section (130 sections) In total 41 foci were observed 2 of which were portal, 39 being situated in the parenchyma Out of these there [illegible] ubtubercles
> [illegible] II is portal
> [illegible] type II, it
> is neither an ordinary tubercle nor a scar, but belongs to an intermediate type
>
> *Conclusion* 41 subtubercles predominantly of type IV, and relatively recent

The last biopsy showed that the process was still active, though both the E S R and the temperature had become normal Consequently the patient was advised to continue bed-rest and P A S treatment at home He is at present in excellent health

In view of the positive findings in the liver tissue of the above patients, who were seriously ill and had high temperatures, a strong case could be made out for regular examination of the C S F, lest the earliest stages of meningitis be missed That this was not done in our patients was due to the fact that at that time our insight into the pathogenesis of the different forms of tuberculosis was not yet sufficiently adequate At present our views have so far been modified that we believe that the necessity of a regular examination of the C S F depends in most cases on the clinical symptomatology, but that in miliary tuberculosis (i e when a miliary picture is visible on the roentgenogram) examination of the C S F should be done at regular intervals independently of the patient's general clinical condition

CHAPTER V

ERYTHEMA NODOSUM AND ERYTHEMA INDURATUM (BAZIN's DISEASE)

ERYTHEMA NODOSUM

Erythema nodosum is a more or less transient "allergic" reaction *in which the skin responds to toxins present in the blood stream* These toxins may be derived from a bacterium or a virus or from some chemical substance of exogenous origin This is a *non-specific syndrome, whose pathogenesis is at present* anything but certain There is no doubt that in medical literature too much stress has been laid on the attempt to find a definite aetiology for *every case of erythema nodosum, but we are safe in saying that* the origin of these lesions cannot always be traced to tuberculous infection, although (in Europe at least) this aspect requires especial *attention in the majority of cases*

In the first place we wish to lay stress on the use of aspiration liver biopsy in any individual case of erythema nodosum in which a tuberculous origin is suspected From clinical statistics it has long been known that erythema nodosum of this type must be ascribed to a haematogenous dissemination of tubercle bacilli This fact stimulated us to perform liver biopsy in such cases, as we believe that tubercles will be found in the liver in practically all cases of haematogenous tuberculosis

In 14 out of 20 cases of erythema nodosum in which we have performed aspiration liver biopsy tubercles were demonstrated in the liver tissue, so that the diagnosis of granulomatous disease could be arrived at with a degree of probability bordering on certainty (Table II)

9 out of the 14 patients with positive biopsy showed enlarged hilar nodes on chest X-ray examination No such changes were

found in X-rays of the 6 patients with negative biopsies 12 of these 14 cases with positive liver biopsies were on clinical grounds diagnosed as tuberculosis, 2 as sarcoidosis

In one of the two cases which on clinical grounds were diagnosed as relapsing acute rheumatic fever and in one also of two cases similarly diagnosed as chronic rheumatoid arthritis one subtubercle of type IV was found, but we have not yet enough experience to interpret this observation In two cases in which the liver biopsy was negative it proved impossible to arrive at a diagnosis on clinical grounds

In the second place, since in cases with a positive biopsy we have irrefutable evidence of blood-spread tuberculous infection, and since we believe that haematogenous dissemination is the principal indication for antibiotic and chemotherapeutic treatment in tuberculosis, it would appear to be logically necessary to institute such therapy in these cases also Up to the present, however, we have avoided the rigid view that every patient with this clinical picture should be subjected to streptomycin treatment, if necessary combined with chemotherapeutics, such as P A S , isoniazid or (a few years ago) sulphetrone or promin, remembering not only that it is possible for streptomycin to cause serious toxic symptoms, but that there is also the possibility of the tubercle bacilli becoming resistant, so that such agents could no longer be used in the treatment of later more serious recurrence of the infection It appeared, however, that the use of a combination of agents reduces the chance of development of drug-resistance by the tubercle bacilli The view that every patient with erythema nodosum of tuberculous origin should be treated actively with streptomycin and other drugs is, however, supported by statistics drawn up by MASCHER, who reported that 25 % of his patients later developed active pulmonary tuberculosis and a further 25 % developed active tuberculosis elsewhere

For the present, we believe that therapy should be decided after full clinical assessment of the individual case, considering especially such factors as fever, the general state of nutrition,

general symptoms and age This position may be modified by the discovery of safer and more active remedies against tuberculosis in the future

The following case illustrates our views

CASE HISTORY

Case I Miss v d S 1177/1948 aged 13 was admitted to hospital acutely ill with a high temperature and erythema nodosum on the extensor aspect of the arms and legs

Apart from the extensive skin lesions on the extremities nothing significant could be found on examination The erythrocyte sedimentation rate was 87 mm during the first hour and 1 3 mm during the second hour The differential leucocyte count showed slight toxic changes No abnormality could be found in the urine The tuberculin test (VON PIRQUET) was strongly positive Chest X ray showed a left hilar shadow which on tomographic examination proved to be due to enlarged hilar glands Repeated examination of stomach washings failed to yield tubercle bacilli

Aspiration liver biopsy was performed in order to confirm the probabl diagnosis of tuberculosis The pathological report read as follows

> The biopsy measured 4 cm long and was examined in serial section (?00 sections) In total 16 tubercles were found 5 of them being situated in portal tracts and 11 in the parenchyma Of these 1 belongs to type I 12 to type II _ to type III and 1 to type IV They are all epithelioid without any necrosis or fibrinous exudate and without giant cells Among the epithelioid cells there are lymphocytes neutrophils and eosinophils
>
> *Conclusion* multiple young submiliary epithelioid-cell tubercles and subtubercles without necrosis or giant cells extensive haematogenous dissemination

The clinical picture of a seriously ill patient combined with the positive liver biopsy decided us in favour of streptomycin treatment we hoped to eliminate the active foci as soon as possible and to prevent new disseminations Two weeks after the beginning of the streptomycin therapy (i e a little over six weeks after admission) a second biopsy was performed The pathological report read as follows

> The biopsy (one sixth the size of the previous material) was examined in serial section (100 sections) There is slight fatty infiltration in the periportal parenchyma An occasional eosinophil leucocyte is ob

served in the capillaries We found one submiliary tubercle of type I, without necrosis or fibrin, and without giant cells it lay in a portal tract The young fibroblasts, of a slightly older type than previously, are surrounded by lymphocytes and occasional eosinophils In addition a minute round epithelioid-cell focus with an eosinophil leucocyte, and a small ill-defined type III focus consisting of young fibroblasts, lymphocytes and eosinophil leucocytes were seen in the parenchyma *Conclusion* haematogenous dissemination of a slightly older type than the first biopsy"

As it happened fever had remitted partly just before therapy was commenced, but during therapy the patient's general condition improved rapidly, her weight increased and the temperature remained subfebrile Eight weeks after the commencement of the streptomycin therapy a third biopsy was performed The pathological report read as follows

"The biopsy measured 2 cm long and was examined in serial section (104 sections) Only 5 small foci of type IV were found These foci may be a later stage of development of the subtubercles seen in the former biopsies There is slight fatty infiltration and a trace of periportal nuclear glycogen *Conclusion* five minute subtubercles in the parenchyma Slight fatty infiltration"

Before the patient was discharged at the end of the streptomycin therapy a fourth biopsy was performed Three and a half months had elapsed since the first biopsy The pathological report read as follows

"The biopsy measured 3 8 cm long and was examined in serial section (108 sections) There is slight to moderate fatty infiltration (slightly more than in the two previous biopsies) Some nuclear glycogen is found in the periportal areas Fourteen foci are observed eight of which are portal Among them there are five portal scar balls (1 of type I 3 of type II and 1 of type III) two of which are already hyalinized There are also in the same site a small tubercle of type III consisting of older connective tissue and two relatively young tubercles of type II in which there are some eosinophil leucocytes In the parenchyma three older and two younger subtubercles of types III and IV and a small young focus of type IV were observed *Conclusion* multiple relatively young tubercles apart from the older and the completely cicatrized tubercles which are partly hyalinized There is some fatty infiltration

The patient was advised to continue the rest-cure at home combined with good nutrition and extra vitamins After three months she was again admitted for a follow-up examination Her condition was excellent No abnormalities were found The erythrocyte sedimentation rate was 13 mm

during the first hour, and 32 mm during the second hour Chest X-ray still revealed enlargement of the hilar nodes on the left, but the shadow was better defined A fifth liver biopsy was performed in order to determine objectively whether the process had really subsided Since the first biopsy seven months had now elapsed The pathological report read as follows

"The biopsy measured 2 1 cm long, and was examined in serial section (111 sections) There is no trace of fresh dissemination As could be expected, there are scars of previous lesions In the parenchyma four foci of type III and IV, of medium age, and three portal hyaline scars were found Although not of practical importance, it is worth mentioning that we observed hyperaemia, a trace of lipofuscin (pericentrally) and a trace of nuclear glycogen (periportally) The fatty infiltration, seen during and shortly after the streptomycin therapy, has disappeared again Only a very rare fatty vacuole could be observed.

Conclusion some remains of older lesions, but no fresh dissemination"

The process was therefore proved to have come to a standstill The patient was allowed to return very gradually to full activity Rather more than a year after leaving hospital the chest X-ray showed an infiltration in the left middle zone and she was treated with bed-rest and P A S per os for about a year At the moment of writing about $2^1/_2$ years after her complete recovery, she is well

We would further refer the reader to our preliminary report elsewhere concerning liver changes in cases of erythema nodosum (see bibliography)

ERYTHEMA INDURATUM (BAZIN'S DISEASE)

We have examined liver biopsies in four cases of this disease All were positive The following will serve as an example

CASE HISTORY

Case VI Miss v M 538/1949 aged 23, came to our outpatient department complaining of a red indurated area on the legs below the knees The dermatologist diagnosed erythema induratum The young lady's fiance was known to suffer from tuberculosis Apart from obesity nothing significant could be found on general examination The erythrocyte sedimentation rate was 8 mm during the first hour, and 41 mm during the second hour The differential leucocyte count revealed nothing of note The tuberculin test (VON PIRQUET) was positive

In order to determine the cause of the condition it was decided to perform an aspiration liver biopsy. The pathological report read as follows:

"The biopsy measured 2 cm. long, and was examined in serial section (130 sections). 25 foci were seen. They are all still young: 3 being situated in the portal areas, and 22 in the parenchyma. One of them is of type I, 3 are of type II, 5 of type III, and 16 of type IV. There is no necrosis. In two foci there is a certain amount of fibrin. There are some giant cells, neutrophils, and lymphocytes. No eosinophils can be found. There is a fatty infiltration of the liver parenchyma.

Conclusion: extensive haematogenous dissemination, which is in an early stage."

Accordingly the patient was treated with streptomycin, P.A.S., and strict bed-rest. After some months the erythema had completely disappeared.

Six months after the first biopsy we performed a second one. The pathological report on the liver tissue read as follows:

"The biopsy measured 1.9 cm. long, and was examined in serial section (108 sections). No submiliary tubercles were observed. In the parenchyma there are a total of 11 subtubercles, some young, some less young and some intermediate. Three of them belong to type III, eight to type IV. There is also a slight fatty infiltration.

Conclusion: partly young, partly older lesions of types III and IV in the parenchyma. Comparison with the previous biopsy suggested some improvement."

As a result of these findings the patient was advised to continue the rest-cure, in combination with P.A.S. At the last follow-up examination she was in excellent condition.

Biopsies in these four cases were done in the first place as a matter of pure scientific inquiry, but they have taught us that this remarkable skin affection, so different from erythema nodosum, may also be an expression of the haematogenous dissemination of tubercle bacilli. We do not however yet regard ourselves as being on firm enough ground to make detailed suggestions for the treatment of this disease.

during the first hour, and 32 mm during the second hour Chest X-ray still revealed enlargement of the hilar nodes on the left, but the shadow was better defined A fifth liver biopsy was performed in order to determine objectively whether the process had really subsided Since the first biopsy seven months had now elapsed The pathological report read as follows

"The biopsy measured 2 1 cm long, and was examined in serial section (111 sections) There is no trace of fresh dissemination As could be expected there are scars of previous lesions In the parenchyma four foci of type III and IV, of medium age, and three portal hyaline scars were found Although not of practical importance, it is worth mentioning that we observed hyperaemia, a trace of lipofuscin (pericentrally) and a trace of nuclear glycogen (periportally) The fatty infiltration, seen during and shortly after the streptomycin therapy, has disappeared again Only a very rare fatty vacuole could be observed

Conclusion some remains of older lesions, but no fresh dissemination"

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In order to determine the cause of the condition it was decided to perform an aspiration liver biopsy The pathological report read as follows

"The biopsy measured 2 cm long, and was examined in serial section (130 sections) 25 foci were seen They are all still young, 3 being situated in the portal areas, and 22 in the parenchyma One of them is of type I, 3 are of type II, 5 of type III, and 16 of type IV There is no necrosis In two foci there is a certain amount of fibrin There are some giant cells, neutrophils, and lymphocytes No eosinophils can be found There is a fatty infiltration of the liver parenchyma *Conclusion* extensive haematogenous dissemination, which is in an early stage"

Accordingly the patient was treated with streptomycin, P A S, and strict bed-rest After some months the erythema had completely disappeared Six months after the first biopsy we performed a second one The pathological report on the liver tissue read as follows

"The biopsy measured 1 9 cm. long, and was examined in serial section (108 sections) No submiliary tubercles were observed In the parenchyma there are a total of 11 subtubercles, some young some less young, and some intermediate Three of them belong to type III, eight to type IV There is also a slight fatty infiltration *Conclusion* partly young partly older lesions of types III and IV in the parenchyma Comparison with the previous biopsy suggested some improvement"

As a result of these findings the patient was advised to continue the rest-cure, in combination with P A S At the last follow-up examination she was in excellent condition

Biopsies in these four cases were done in the first place as a matter of pure scientific inquiry, but they have taught us that this remarkable skin affection, so different from erythema nodosum, may also be an expression of the haematogenous dissemination of tubercle bacilli We do not however yet regard ourselves as being on firm enough ground to make detailed suggestions for the treatment of this disease

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> "The biopsy measured 2 1 cm long, and was examined in serial section (111 sections) There is no trace of fresh dissemination As could be expected there are scars of previous lesions In the parenchyma four foci of type III and IV, of medium age and three portal *hyaline scars were found* Although not of practical importance, it is worth mentioning that we observed hyperaemia, a trace of lipofuscin (pericentrally) and a trace of nuclear glycogen (periportally) The fatty infiltration, seen during and shortly after the streptomycin therapy, has disappeared again Only a very rare fatty vacuole could be observed
>
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leucocytes being 8 000 per c mm The urine was normal The tuberculin reaction (VON PIRQUET) was negative though according to the patient it had been positive on an earlier occasion On examining the cerebrospinal fluid the pressure proved to be 31 mm the number of cells was 308/c mm almost entirely lymphocytes The NONNE and PANDY reactions were positive The glucose content was 40 mg % No tubercle bacilli were found on microscopical examination Chest X-ray revealed the picture of miliary tuberculosis Tubercles were observed also in the optic fundus

In order to confirm this diagnosis and as a control for a second biopsy planned to follow treatment, it was decided to perform an aspiration liver biopsy The pathological report read as follows

'The biopsy measured 1 3 cm long and was examined in serial section (114 sections) 78 sections were stained with haematoxylin-eosin and 36 according to HALLBERG In total 80 foci were observed 3 of type I 16 of type II 5 of type III and 56 of type IV These tubercles are predominantly young though some belong to an intermediate type 17 are located in the portal spaces and 63 in the parenchyma There is some fibrin and a trace of caseation in the larger tubercles There are many giant cells of various types lymphocytes and neutrophils Twelve acid-fast rods are seen six of them ingested by giant cells

Conclusion subacute haematogenous tuberculosis

Following this positive result streptomycin was administered both intramuscularly and intrathecally in combination with promin A considerable improvement resulted the erythrocyte sedimentation rate remained normal and after three weeks the temperature was subfebrile The tubercles in the optic fundi were seen to be becoming fibrotic

A second biopsy was performed nearly two months after the first The pathological report read as follows

The biopsy measured 2 4 cm long and was examined in serial section (120 sections) In total 66 foci were found 13 of them in the portal spaces and 53 in the parenchyma Types O and I are lacking 15 foci belong to type II 10 to type III and 41 to type IV Those that belonged to type I in the first biopsy have shrunken down into type II in the second Necrosis or fibrin are nowhere to be observed There are a few giant cells neutrophils and eosinophils besides lymphocytes The foci of type IV are often young Among the larger tubercles the intermediate type prevails

Conclusion there is still an extensive haematogenous dissemination but fewer foci and there is a shift to a somewhat older type as compared with the previous biopsy

CHAPTER VI

MILIARY TUBERCULOSIS

Aspiration liver biopsy has been performed in sixteen cases of miliary tuberculosis In each of these cases the clinical picture and the chest X-ray, taken together, had been enough to establish beforehand the probable diagnosis of miliary tuberculosis In every case tubercles (of types I to IV inclusive) were found in the liver in twelve there was caseation In such cases of frank miliary tuberculosis the degree of haematogenous dissemination is so great that tubercles can nearly always be found in the biopsy without having resort to serial sections HALLBERG staining was done in ten cases and acid-fast rods found in nine of these (in necrotic material sometimes but more often in near-by giant cells) Previous streptomycin treatment accounted for the one negative case and in the patient concerned tubercle bacilli were later grown from genito-urinary lesions Of the nine cases in which the bacilli were demonstrated in the liver biopsy seven also yielded bacilli in cultures from the sputum stomach washings or cerebrospinal fluid (three times before the liver biopsy and four times after it) In two cases the liver biopsy was the only material in which bacilli were found

We give details of two of our cases

CASE HISTORIES

Case I II Miss v 4 S 71/1949 aged 17 complained of violent headach for a fortnight On the day of her admission she became sick and vomited Since the onset she had had fever (about 38 9° C) Physical examination yielded the clinical picture of tuberculosis Percussion revealed an enlarged spleen There was neck rigidity The erythrocyte sedimentation rate was 10 mm during the first hour and 2 mm during the second hour The differential ll count revealed slight toxic changes the total number of

The patient's sputum was found to contain acid fast rods In view of the swelling of the ankle a synovial biopsy was done The pathological report read as follows

The capsular tissue was examined in serial section Of the 132 sections 80 were stained with haematoxylin-eosin and 52 according to HALLBERG The material proves to be subchronic tuberculous granulation tissue i e relatively young vascular connective tissue with many lymphocytes and plasma cells a few neutrophils and with many miliary and submiliary tubercles with giant cells (of both osteoclastoma and LANGHANS types) and occasionally a trace of necrobiosis/necrosis On staining with night blue 79 acid fast rods were observed 22 of which were located in giant cells

Conclusion subchronic tuberculous granulation tissue

Guinea pig inoculation with a portion of the capsular tissue confirmed the presence of tuberculosis

The patient was treated with streptomycin promin and P A S After two months of treatment evidence of meningitis appeared The C S F pressure was 24 cm the glucose content was 21 mg % NONNE's test was negative and PANDY's positive The number of cells was 248 per c mm chiefly lymphocytes In view of these findings additional streptomycin was administered intrathecally Cultures of C S F were negative

Eighteen days after meningitis had been diagnosed a second aspiration liver biopsy was performed The pathological report read as follows

The biopsy measured 1 5 cm long and was examined in serial section (110 sections) In total 43 foci were observed 9 of them portal and 34 in the parenchyma Three of them are of type I 4 of type II 11 of type III and 25 of type IV The tubercles of types I and II are cicatrizing Their centres are still active sometimes containing a giant cell of the LANGHANS or osteoclastoma type but they are completely or partially encapsulated the capsule being sometimes incomplete Fibrin and necrosis are absent Eosinophil leucocytes are not seen but a few neutrophils are present The foci of types III and IV are predominantly of the large-cellular type

Conclusion haematogenous dissemination considerably less dense than in the first biopsy The larger tubercles are cicatrizing

This indicated clearly that the process outside the central nervous system had receded to a considerable extent Meanwhile the miliary shadows on the chest X ray had disappeared Because of the meningitic symptoms it was decided to continue the intrathecal streptomycin treatment in combination with P A S and promin for a considerable period Three years after the onset of the illness the patient was considered as completely

The patient's condition continued to improve The C S F continued to show a few lymphocytes this persistent slight pleocytosis may well have been caused by the intrathecal administration of the streptomycin Four months after admission the miliary shadows on the chest X-ray had disappeared

In view of the positive liver biopsies, the clinical picture, and the fact that in the meantime positive cultures had been obtained from the C S F and the liver, it was decided to proceed to a very long period of intrathecal administration of streptomycin About three years after the onset of the illness the patient was considered as completely recovered and now, two years afterwards, she is in an excellent health. During 14 months she had been treated with streptomycin, administered intrathecally, and during two years she had received P A S per os

Case VIII Miss B 291/1949, aged 26, was admitted at the request of a consultant physician because diffuse miliary shadows had been found in her chest X-rays She had developed a painful swelling of the right ankle after injury, and the chest condition had come to light during investigation of this There were no other complaints On physical examination there were fine crepitant rales scattered through both lungs Apart from a swollen ankle there were no further abnormalities There were no symptoms of meningitis The erythrocyte sedimentation rate was 3 mm during the first hour, and 7 mm during the second hour The differential cell count was normal The urine did not reveal anything of note The tuberculin reaction (von PIRQUET) was positive On admission there was a subfebrile temperature

In order to confirm the diagnosis of miliary tuberculosis and to determine the extent of the process, if possible, it was decided to perform an aspiration liver biopsy The pathological report read as follows

"The biopsy measured 1 6 cm long and was examined in serial section (110 sections) 60 sections were stained with haematoxylin-eosin, and 50 according to HALLBERG In the 60 sections stained with haematoxylin-eosin there are 146 foci, 11 of which are of type I, 6 of type II, 39 of type III and 90 of type IV All the tubercles of type I are caseating and lie in the portal spaces There are many giant cells of the osteoclastoma type and the foreign body type The 6 tubercles of type II are also portal and they are partly caseating The lesions of types III and IV have epithelioid cells and are situated in the parenchyma The cell type suggests a fairly recent dissemination Neutrophils are observed in addition to the lymphocytes In the 50 sections that were stained according to HALLBERG 9 acid-fast rods (6 in giant cells, and 3 in necrotic tissue) were found

Conclusion extensive partly caseating haematogenous tuberculosis of fairly recent origin"

or sarcoidosis Although negative findings do not completely exclude these diseases we are justified by the clinical and pathological data in believing that the entire picture was due to mitral stenosis

As a second point in considering the value of liver biopsy in these cases, the histological structure of the tubercles may give us some idea of the activity of the process We are often misled in this matter by the clinical symptoms, the erythrocyte sedimentation rate the blood picture, the temperature chart, etc In the third place it is possible that the tuberculogram we mentioned in Chapter II may supply us with an objective picture in assessing the value of modern therapeutic agents In this it is of especial value to be able to compare the histological picture of a first biopsy with that of the subsequent specimen or specimens In the fourth place it is possible to examine the liver tissue bacteriologically We shall revert to the importance of this later

In the fifth place one may find indications for the carrying out of a lumbar puncture The presence in the liver biopsy of submiliary tubercles and subtubercles in such numbers that they can be found at once without serial sections must raise a strong suspicion that many submiliary and perhaps also miliary foci (possibly latent) are present not only in the liver and the lungs but elsewhere in the body as well in other words they may also be already established in the cerebral cortex and the meninges which are so difficult to reach by antibiotic therapy In view of these considerations and after we had seen a tuberculous meningitis develop in two patients during treatment with streptomycin we nowadays perform lumbar puncture regularly (once a month) in all patients suffering from miliary tuberculosis At the slightest suspicious sign (increase of lymphocytes and reduction of glucose in the C S F) they are treated as cases of tuberculous meningitis So far this has taken place three times We look upon the neurologist s fear that tuberculous meningitis may be lit up by lumbar puncture as obsolete

Finally we would point out that with the aid of modern therapeutic agents the miliary shadows on the chest X-rays disappear as a rule in two to five months

recovered At the moment of writing, two further years later, she is in an excellent health During 13 months she had been treated with streptomycin administered intrathecally and during 15 months she had received P A S per os

What is the clinical value of the aspiration liver biopsy in these cases? In the first place, it is possible to make an early diagnosis without having to wait for the culture of tubercle bacilli (which sometimes takes up so much time), even though direct microscopic examination of the sputum, urine, pus or other material for tubercle bacilli is negative. Further it is clear that this technique may be of especial value in the differential diagnosis of miliary shadows in the lungs where several conditions (pulmonary carcinomatosis, cardiac insufficiency, pneumoconiosis, syphilis) may prove indistinguishable from miliary tuberculosis The absence of tubercles from the liver in such cases is, in our opinion, strong evidence against the diagnosis of miliary tuberculosis The following case may serve as an example

CASE HISTORY

Case IX Mr T, aged 23, complained originally of haemoptysis He recovered after a rest-cure He had never been seriously ill, and had no history of acute rheumatism On physical examination clear evidence of mitral stenosis was found There were no enlarged lymph glands The spleen and liver were enlarged and easily felt There were no other abnormalities The blood pressure was normal The urine was normal The erythrocyte sedimentation rate was 41 mm during the first hour The WASSERMANN reaction was negative The VON PIRQUET and MANTOUX reactions were negative

Fluoroscopic examination of the chest revealed hilar enlargement and finely granular lung fields If the heart shadow had not shown to a slight degree the shape peculiar to mitral stenosis, the whole picture would have seemed wholly typical of tuberculosis or sarcoidosis At the health centre the diagnosis of tuberculosis or sarcoidosis was seriously considered The palpable spleen might have pointed to either of these diseases, or to mitral stenosis (probably rheumatic in origin)

The patient was admitted for an aspiration liver biopsy In the biopsy material (serially sectioned) we were able to find a distinct stasis but there was no centrilobular fibrosis There were no traces of tuberculosis

or sarcoidosis Although negative findings do not completely exclude these diseases, we are justified by the clinical and pathological data in believing that the entire picture was due to mitral stenosis

As a second point in considering the value of liver biopsy in these cases, the histological structure of the tubercles may give us some idea of the activity of the process We are often misled in this matter by the clinical symptoms, the erythrocyte sedimentation rate the blood picture, the temperature chart, etc In the third place, it is possible that the tuberculogram we mentioned in Chapter II may supply us with an objective picture in assessing the value of modern therapeutic agents In this it is of especial value to be able to compare the histological picture of a first biopsy with that of the subsequent specimen or specimens In the fourth place it is possible to examine the liver tissue bacteriologically We shall revert to the importance of this later

In the fifth place, one may find indications for the carrying out of a lumbar puncture The presence in the liver biopsy of submiliary tubercles and subtubercles in such numbers that they can be found at once without serial sections must raise a strong suspicion that many submiliary and perhaps also miliary foci (possibly latent) are present not only in the liver and the lungs, but elsewhere in the body as well, in other words they may also be already established in the cerebral cortex and the meninges which are so difficult to reach by antibiotic therapy In view of these considerations, and after we had seen a tuberculous meningitis develop in two patients during treatment with streptomycin, we nowadays perform lumbar puncture regularly (once a month) in all patients suffering from miliary tuberculosis At the slightest suspicious sign (increase of lymphocytes and reduction of glucose in the C S F) they are treated as cases of tuberculous meningitis So far this has taken place three times We look upon the neurologist s fear that tuberculous meningitis may be lit up by lumbar puncture as obsolete

Finally we would point out that with the aid of modern therapeutic agents the miliary shadows on the chest X-rays disappear as a rule in two to five months

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CHAPTER VII

TUBERCULOUS MENINGITIS

Aspiration liver biopsy was performed in fourteen cases of tuberculous meningitis In thirteen of them we observed tubercles in the liver tissue The only negative case was that of a patient from another town, whose liver biopsy was sent to us for examination The chest X-ray was clear in this case, but later tubercle bacilli were cultured from the cerebrospinal fluid on one occasion only After the conclusion of streptomycin treatment a relapse occurred causing the patient's death five months after the onset of his disease Autopsy was not possible, and unfortunately no liver biopsy was done postmortem In eight of the positive cases there was also generalized blood-spread miliary tuberculosis with its characteristic chest X-ray

The clinical importance of the aspiration liver biopsy in meningitis may briefly be summed up as follows The prospect of the major therapeutic procedures which must follow the diagnosis of tuberculous meningitis especially the prolonged intrathecal administration of streptomycin compels us to seek a positive diagnosis at the earliest moment It is not always easy to arrive at this diagnosis with certainty by examination of the cerebrospinal fluid alone Lymphocytosis for instance is not by any means an objective proof of the presence of tuberculous meningitis In this respect benign lymphocytic meningitis (virus-meningitis or chorio-meningitis) caused by the ARMSTRONG virus or the herpes zoster virus is particularly important especially in its initial stages when differential diagnosis may be very difficult Personal experience has taught us that the C S F glucose can be equally unreliable Culture of the bacilli is still too often too slow it takes at least six weeks (at any rate in

early cases) before a definite result is attained Irreparable damage may be caused by delaying the therapy while waiting for a certain diagnosis On the other hand, it is possible to camouflage the true nature of the case by proceeding too quickly to intrathecal streptomycin treatment, thus, for instance, a spontaneous improvement may be wrongly ascribed to the streptomycin that has been administered Moreover, later repetition of the bacteriological examination for tuberculosis which may prove necessary may be rendered impossible Besides, intrathecal streptomycin treatment leads to an increase of the number of lymphocytes in the spinal fluid, so that this standard for measuring the activity of the disease is obscured

It goes without saying that these objections do not arise when acid-fast rods are demonstrated by microscopical examination in the veil-like clot formed in the spinal fluid But in other cases it may certainly be looked upon as a gain when liver biopsy supplies either support or a definite result

With regard to the pathogenesis of tuberculous meningitis we would like to draw attention to the following matter The grave clinical picture, with its (failing intrathecal streptomycin) big chance to a fatal outcome (LORBER) derives principally from the repeated infection of the meninges by one or more tuberculous foci (miliary or larger) in the brain substance (RICH and MCCORDOCK MACGREGOR and GREEN) At postmortem it has appeared that this localisation in the brain is usually secondary to a localized often relatively inactive lesion elsewhere in the body, under which heading an important part is played by the hilar and the mediastinal lymph nodes from which haematogenous dissemination so often starts (Chap XII) From experience we know that such partly caseous partly hyalinized lymph nodes may escape attention in the roentgenogram

When meningitis has an origin of this type streptomycin can only affect the tubercle bacilli in the meninges and in the spinal fluid while those in the cerebral focus remain untouched Thus recurrence of tuberculous meningitis is easily understandable In these cases the low activity of the focus of dissemi-

nation accounts for our observation that (except of course in those cases in which the meningitis is merely one manifestation of an overt generalized miliary tuberculosis) the liver biopsy contains only scanty tubercles of the larger sizes (cicatrizing or otherwise) even when types III and IV are common A difficulty might be thought to arise in cases in which lesions of type IV only are present Similar structures can be found in virus meningitis, and it might appear that the liver biopsy will fail to provide the diagnosis in such cases In practice, however, we have found that the trained eye can differentiate the two liver lesions

It is clear that even repeated liver biopsies do not give us a full insight into the course of the process The extra-cerebral disease may subside and this will be mirrored by the liver, but meanwhile the cerebral foci may continue their baleful activity Did not investigations by BAGGENSTOSS, FELDMAN HINSHAW and HEILMAN show conclusively that streptomycin *does not penetrate into the brain tissue while it is present in adequate concentration* in the spinal fluid? One can only hope that a spontaneous cure (possibly with calcification) will take place in the cerebral foci under the influence of bed-rest and good nutrition — in other words the old conservative therapy! Systematic *intrathecal administration of streptomycin is* partly based on the expectation that the tubercle bacilli already present in the spinal fluid will be rapidly attacked, but at the same time it is hoped to deal at once with fresh meningeal disseminations

We will finally submit some general remarks about the streptomycin treatment of tuberculous meningitis It is of the greatest importance to inject the intrathecal streptomycin exceedingly slowly (10 to 15 minutes per injection) RIVOIRE and COLLEAU drew attention *to this mode of injection which prevents* blockage of the subarachnoid space It is very important to be aware of this as continuation of the therapy depends entirely on it A second point to which we would like to draw attention is the necessity of continuing intrathecal streptomycin treatment *for a considerable* period of time Experience with a patient who suffered from tuberculous meningitis for more than a

year has taught us this It is not yet clear why the long continuation of the intrathecal streptomycin treatment is so necessary to success An explanation may perhaps be found in the fact that the cerebral focus which is difficult of access to streptomycin continually discharges streptomycin-sensitive tubercle bacilli into the C S F but the bacilli are again and again rendered harmless by the streptomycin injected intrathecally

Our own experience would suggest that when these two conditions are fulfilled the prognosis of tuberculous meningitis is considerably more favourable than is generally stated in medical literature Out of 12 patients treated with streptomycin and P A S four died and eight are doing splendidly The intravenous administration of P A S-stabilise of DEBAT and of I N H improved the prognosis of tuberculous meningitis enormously (It would take us too far to discuss the significance of A C T H tuberculin hyaluronidase and streptokinase in this connection) We may look upon aspiration liver biopsy as a distinct diagnostic gain in these cases for it is especially in the cases with an early diagnosis that it is possible to obtain a permanent cure provided the above-mentioned conditions are met

CASE HISTORIES

Case I Miss V 1258/1948 aged 27 was admitted to the clinic as a case of meningitis Six weeks previously she had had a miscarriage losing a large quantity of blood Against her doctor s orders she made a trip on a motor-cycle after this miscarriage on this trip she was said to have contracted pneumonia and was confined to bed for three weeks Her temperature was said never to have been above 37° C Two days before her admission she had had a violent headache attended with vomiting The family doctor diagnosed meningitis and advised admission to a hospital

On admission there was a slight stiffness of the neck BRUDZINSKY s signs I and II however were both negative The left pupil was decidedly larger than the right and the right pupil was not exactly round On palpation small swollen lymph nodes were found in the neck, axillae and groins. The heart was of normal size the heart sounds loud but clear Neither liver nor spleen was enlarged. There were no further physical findings

On the roentgenogram of the thorax a diffuse and even distribution of small focal shadows was observed the radiologist believed he had to

do with miliary tuberculosis or with sarcoidosis The temperature was intermittent in character and fluctuated between 37° C and 39 5° C The red cell sedimentation rate was 60 mm. during the first hour, and 83 mm during the second hour The differential cell count showed neutrophil leucocytosis with primitive forms and toxic granulation, eosinophil leucocytes were lacking In the urine there was a trace of albumin but there were no reducing substances in the sediment two or three leucocytes per visual field were found The VON PIRQUET was negative, the MANTOUX positive at 1 1000 The luetic reactions were very decidedly positive

On the day of admission the patient had an epileptic attack in the hospital The neurologist who was called into consultation after considering the results of the examination of the spinal fluid and the chest X-ray thought he had to do with tuberculous meningitis with a right sided cerebral focus Examination of the spinal fluid yielded the following facts The number of cells was 48 cells per c mm predominantly lymphocytes The protein content was increased The colloidal gold reaction was abnormal (0123322211) The glucose content was 0 065 %. No bacteria were found in the GRAM specimen and the web of fibrin did not yield any tubercle bacilli A guinea-pig test afterwards proved to be negative

As a result of this diagnosis even though it was not confirmed bacteriologically it was decided to commence intensive streptomycin treatment The drug was injected intrathecally (0 1 gm a day) and intramuscularly (2 4 gm a day) After twelve days the intrathecal administration of streptomycin was discontinued after which an improvement was noted in the temperature curve After four weeks the intramuscular administration was discontinued for a period of nineteen days because the patient vomited continually (intoxication?)

As the diagnosis had not been confirmed bacteriologically, it was decided ten days after admission to perform a liver biopsy The pathological report read as follows

The biopsy measured 1 6 cm long and was examined in serial section (150 sections) In total 13 tubercles were found 11 of which were portal and two parenchymal One belongs to type I 11 to type II and 1 to type IV In one tubercle we noted the commencement of caseation and two showed a trace of fibrin There are many giant cells of various types Besides lymphocytes we observed some neutrophils and an occasional eosinophil 42 sections were stained according to HALLBERG and two acid fast rods found in them No spirochetes were demonstrated in LEVADITI-stained material

Conclusion subacute non-caseating submiliary tuberculosis Guinea-pig test inoculation with a portion of the biopsy material afterwards proved positive

During treatment with streptomycin there developed a neurological picture with papilloedema, which was explained by the neurologist as a consequence of persistent basal meningitis with arachnoiditis optica Because of the high pressure of the spinal fluid he thought also of the possibility of internal hydrocephalus As the papillae seemed to be becoming atrophic, it was decided to dehydrate with $MgSO_4$, in order to reduce the cerebrospinal pressure This treatment failed, and trephining, which was at first rejected, was considered necessary as a last resort The patient was therefore removed to the department of neurosurgery in Utrecht At that moment she had undergone streptomycin treatment for a period of four months

Dr VERBIEST performed ventriculography, and found a displacement of the ventricular system to the left The line of the septum ventriculorum was somewhat concave towards the right Dr VERBIEST could only decide with certainty on an oedema of the right hemisphere, and he therefore resolved to perform a subtemporal decompression only The examination of the fluid obtained at that time yielded the following results The NONNE and PANDY reactions were negative, the fluid containing only 7/3 cells per c mm The colloidal gold curve was normal

After a seventeen days' stay in the hospital in Utrecht the patient was returned to our clinic Physical examination now yielded little, except for the operation scar The reactions of the pupil had become normal A detailed neurological examination did not yield anything of note except a rapid nystagmus on looking towards both sides with a slight rotatory component, and a slight secondary atrophy in the optic papillae The

she had been through, the patient was now in a very good condition In order to obtain an idea of the influence of the streptomycin on the miliary tuberculosis, roentgenograms of the chest were again made, the radiologist was of the opinion that the miliary shadows in the lungs had become less well-defined The lungs gave an impression of decreased activity

At the same time a second liver biopsy was performed, seven months after the first The pathological report read as follows

'The biopsy measured 1 3 cm long 84 serial sections were examined, 60 of them stained with haematoxylin and eosin, 12 stained with VAN GIESON, and 12 according to HALLBERG Only 8 foci were observed, two of which were in a portal position, and six in the parenchyma One is of type I, 1 of type II, and 6 of type IV Necrosis, fibrin, giant cells and leucocytes are absent No acid-fast rods can be found One of the portal foci is unusual, consisting of a central area of

lymphocytes and some fibrocytes enclosed by homogeneous hyaline
Conclusion cicatrizing submiliary tubercles and a few subtubercles
In view of the concomitant lues the patient received penicillin treatment The result of this of course cannot yet be ascertained After this treatment the patient was discharged in very good condition and is at present in excellent health

Case XI Mr v d B 338/1948 aged 19 was admitted complaining of headache present for about ten days and becoming worse His family believed that they had noticed something strange in his behaviour Three and a half weeks earlier the patient had had a cough.

Physical examination showed a meningeal syndrome The left pupil was smaller than the right There was ptosis of the left eyelid. The roentgenogram of the chest did not reveal any irregularities The erythrocyte sedimentation rate was 9 mm during the first hour and 30 mm during the second hour The white cell count showed leucocytosis and there were toxic changes of the segmented leucocytes Eosinophils were lacking The urine was normal The spinal fluid was clear and it contained almost exclusively mononuclear leucocytes (980 cells per c mm) The NONNE and PANDY reactions were positive In the GRAM stained specimen no bacteria were observed Tubercle bacilli were demonstrated in the web of fibrin The tuberculin test (VON PIRQUET) was positive

The patient underwent intensive treatment with streptomycin 1 7 gm a day was administered intramuscularly and 0 1 gm a day intrathecally Neurological examination showed that we were probably faced with medullar lesions with involvement of the right pontine optic centre After some time the otologist noted that (possibly owing to the influence of streptomycin treatment) the vestibular apparatus on both sides no longer responded to caloric stimuli which, however in view of the patient s serious condition did not justify us in discontinuing streptomycin treatment ~8 days after the commencement of the streptomycin therapy a liver biopsy was performed. It could for obvious clinical reasons not be done at first The pathological report read as follows

The biopsy measured 1 1 cm long and was examined in serial section (108 sections) In total only four very small subtubercles of type IV were found We noted a diminution in the amount of glycogen

In spite of intensive streptomycin treatment the condition of the patient slowly deteriorated After the temperature had risen to 4?° C he died forty days after admission to the clinic Immediately after his death liver biopsy was repeated The pathological examination of the liver tissue resulted in the following report

It was a crumbly biopsy 1 cm of which was cut in serial sections

(195 sections) Only one peculiar submiliary portal tubercle of type I of a very unusual type was found Peripherally it consisted of hyaline connective tissue centrally of lymphocytes and a single large giant cell whose nuclei were placed in the shape of an egg (this remarkable feature could only be recognised in serial sections) With HALLBERG's staining method no acid fast rods were found in this tubercle The liver parenchyma contained no glycogen its cells were dissociated and atrophied Pericentrally there was lipofuscin and hyperaemia

Conclusion a sclerotic portal tubercle

The autopsy (Department of pathology M VAN WIJHE) confirmed the clinical diagnosis of basal tuberculous meningitis No caseous focus was found in the brain The lymph nodes in the right hilus proved to be partly hyalinized partly caseated and liquefied In the lungs in the lower lobe on the right some tubercles were observed on microscopic examination they proved to be partly caseous and they were always enveloped by a thick layer of lymphocytes In the macroscopically normal liver and spleen many sclerosed tubercles were observed and in the former organ they were seen in the portal tracts

Case XII Mr B 1012/1949 aged 19 whose behaviour during the last year had been peculiar (refused to say anything for four weeks listless unwilling highly emotional) complained of continual headache and loss of concentration when studying He also complained of bad eyesight Four weeks before admission he had a period of fever lasting two weeks The headache increased during this period he was very restless and com plained of sleeplessness There was then a short relapse accompanied by a rubeola like rash Three days before admission the temperature was again raised with headache vomiting and increasing confusion

On physical examination no abnormalities could be found apart from obvious neurological symptoms The case was at first thought by our neurologist to be one of encephalitis No improvement was however noticed after treatment with sodium salicylate and absolute bedrest Th consulting ear nose and throat specialist could find no aural lesions Th ophthalmologist reported signs of early papilloedema The neurologist c Utrecht (Dr VERBIEST) who was consulted then suggested the possibili of a meningoencephalitic process perhaps of tuberculous origin

The cerebrospinal fluid contained 704 cells per c mm mostly lymph cytes The glucose content was 50 mg % while the bloodsugar was mg % NONNE's reaction was negative and PANDY's positive On mic scopical examination no tubercle bacilli could be demonstrated Cul was sterile The colloidal gold reaction was normal

The possibility of tuberculosis having been raised an aspiration liver biopsy was performed The pathological report read as follows

The biopsy measured 2 6 cm long and was examined in serial section (100 sections) Only three rather young subtubercles of type IV were observed

Conclusion Three rather young subtubercles of type IV suspicious of tuberculosis

On the above findings a diagnosis of probable tuberculosis was made It was then decided to begin treatment with streptomycin which was administered by the intramuscular (1 gm per day) and intrathecal (100 mg per day) routes combined with P A S 20 gm per day per os After seven weeks the intrathecal dose was reduced to 50 mg per day Six weeks later the guinea pig inoculation of the spinal fluid was reported to be positive

The patient is now — five years after admission — in very good condition The cerebrospinal fluid became normal and the above mentioned treatment was stopped after the completion of one year

Case XIII Miss D 141/1948 aged 17 was admitted complaining of suc violent headache and vomiting On physical examination we found si of meningitis and definite herpes zoster on the left buttock In the cereb. spinal fluid we noted an increased number of lymphocytes the glucc content was normal The erythrocyte sedimentation rate was 35 mi during the first hour and 68 mm during the second hour The bloo picture showed slight toxic changes No changes were found in the urine The tuberculin tests (VON PIRQUET and MANTOUX) were negative (which does not exclude tuberculous meningitis however)

On a presumptive diagnosis of tuberculous meningitis we commenced intrathecal streptomycin administration In order to confirm the diagnosis as soon as possible a liver biopsy was done Examination of the liver biopsy in serial sections did not reveal any tubercles so that the above diagnosis was not supported As the diagnosis of herpes zoster meningitis was becoming more probable the streptomycin therapy was discontinued The patient made a perfect recovery which supported the latter diagnosis

We have observed three other patients in whom we discontinued streptomycin treatment because of a negative liver biopsy These patients also recovered completely confirming our belief that this condition had been one of lymphocytic virus meningitis

The value of the aspiration liver biopsy for the early diagnosis of tuberculous meningitis is demonstrated especially obviously in the third case For further details the reader is referred to a paper published in 1950

CHAPTER VIII

TUBERCULOUS PLEURISY

Aspiration liver biopsy has been performed in fifteen cases of tuberculous pleurisy Here again we have been struck by the fact that a majority of the cases (14) yielded positive results We are therefore justified in looking upon aspiration liver biopsy as an important diagnostic aid in such cases It so often occurs that the pleural effusion containing lymphocytes is found to be sterile and, without aspiration liver biopsy, a diagnosis could then be arrived at on general grounds only The arguments adduced by us in the case of previous groups hold good here also

We are not yet in a position to pass a final judgment on the use of periodic lumbar puncture in these cases When the liver biopsy is strongly positive in a patient suffering from dry pleurisy or from pleurisy with effusion, the clinician may readily imagine himself justified in assuming the presence of a clinically latent focus in the brain also It is hardly necessary to point out, however, that periodic lumbar puncture in all cases has practical objections *In the long run one must rely on the clinical assessment* of the case as a whole for the indications for lumbar puncture That the latent focus may unexpectedly become active, even though the pleurisy is "cured", is a clinical observation which every experienced medical man has made at some time or other The statistical investigations of NATHHORST on pleurisy with effusion in children support the view that antibacterial therapy may be called for From his investigations it is very clear that after pleurisy with effusion the change of subsequent tuberculosis extrapulmonary or pulmonary, is by no means negligible

CASE HISTORY

Case XIV Miss v d M, 644/1948, aged 18, was admitted to hospital suffering from left-sided exudative pleurisy, accompanied by high fever On physical examination a doubtful dullness with impaired breath sounds was found in the left chest *There was displacement of the heart to the right Fluid* was demonstrated by exploratory pleural puncture Many lymphocytes were observed in this exudate, rendering the diagnosis of tuberculous pleurisy probable The erythrocyte sedimentation rate was 65 mm during the first hour and 110 mm during the second hour The blood *picture* revealed slight toxic changes The urine was normal The tuberculin reaction (VON PIRQUET) was strongly positive Chest X-ray showed an *opacity of the left half of the thorax, with considerable displacement of* the heart to the right In view of this displacement paracentesis to the extent of half a litre was performed after some days' interval

In order to support the probable diagnosis of tuberculous pleurisy, and in order to obtain an idea of the activity of the process, an aspiration liver biopsy was performed The pathological report read as follows

"The biopsy measured 2 1 cm long and was examined in serial section (116 sections), 80 sections being stained with haematoxylin and eosin, and 36 by the HALLBERG technique

Twelve foci were found, 10 located in the parenchyma, and 2 in the portal space One belongs to type I (conglomerate tubercle), 2 are of type II, 4 of type III, and 5 of type IV These tubercles are of an unusual type, they are exudative to an exceptional degree, being *hyperaemic with a serofibrinous and cellular (lymphocytic and* leucocytic) exudate, and a few young connective tissue cells There are sporadic, somewhat atypical giant cells No necrosis is observed The smaller foci sometimes lie against the wall of a central vein No *acid-fast rods were found*

Conclusion multiple young submiliary tubercles of an exudative type"

Although the temperature was already falling without any therapy, it was decided, in view of the presence of active haematogenous tuberculosis to proceed to intensive streptomycin treatment On the twenty-fifth day of this treatment there was a return of fever which did not, however exceed 39° In view of this relapse the streptomycin treatment was combined with *promin* The temperature slowly fell again to normal Meanwhile cultures for tubercle bacilli of the fasting gastric contents and the pleural fluid had proved positive After one month of streptomycin treatment during the *second fever phase*, liver biopsy was repeated The pathological report read as follows

The biopsy measuring 2.4 cm long was examined in serial section (120 sections) In total we observed 23 very small round foci consisting of young or slightly older epithelioid cells and lymphocytes 22 of them are situated in the parenchyma and one lies in contact with the portal connective tissue Of these 22 are of type IV 1 is of type III Judged by their nuclei seven are young 14 intermediate and 2 old Necrosis fibrin giant cells or leucocytes were not observed
Conclusion multiple tiny subtubercles in the parenchyma

The fluid in the left pleural cavity slowly resorbed After an initial rise there was a fall in the erythrocyte sedimentation rate The patient s clinical condition improved and three months after the commencement of streptomycin treatment a third liver biopsy was performed The pathological report read as follows

The biopsy measured 3 8 cm long and was examined in serial section (114 sections) We observed 21 foci 4 of which are of type II and portal The remaining 17 are parenchymal subtubercles, 4 being of type III and 13 of type IV Out of the 21 foci 12 are old and 9 are of an intermediate type there are no recent foci Out of the 4 portal foci 2 contain fairly young connective tissue cells surrounded by lymphocytes and a sporadic neutrophil leucocyte The other two consist of lymphocytes among which there are some older connective tissue nuclei and apart from their somewhat oval shape they are not at all typical In none of the foci do we observe necrosis fibrin hyaline or giant cells In contrast with the two previous biopsies there is now slight fatty infiltration
Conclusion Remnants of earlier haematogenous disseminations Slight fatty infiltration

Summing up we may say that the haematogenous dissemination (starting possibly from a primary infection) of which the pleurisy formed a part had probably subsided As the streptomycin therapy had come to an end after treatment of the patient consisted of strict bed rest good nutrition and extra vitamins She is at present in excellent health

CHAPTER IX

TUBERCULOUS PERITONITIS AND ABDOMINAL TUBERCULOSIS

We were able to determine the value of aspiration liver biopsy in this form of tuberculosis in fourteen cases In all cases tubercles were observed in the biopsies when we consider that the affected tissues lie in the drainage area of the portal vein this is not surprising The diagnosis had been considered certain or probable on clinical grounds before biopsy in five of these cases, and had been considered possible in seven In the other two cases the pre-biopsy clinical diagnosis was carcinoma Up to the present as it happens, we have no experience of the contrary process of disproving a clinical diagnosis of tuberculosis

How often the diagnosis of tuberculous peritonitis is missed! How often this diagnosis is needlessly dreaded! How depressing the consequences are in those cases where vague abdominal pains have been present for a long time, and where an X-ray examination has failed to establish its cause! What experienced clinician does not know of cases in which a "malignant tumour" found on palpation of the abdomen or on rectal or vaginal examination has proved at laparotomy or at autopsy, to have a tuberculous aetiology? — or similar cases in which on examination a few months later there proves to be, not an extension but a shrinkage of the palpable mass? Even before the days of modern specific therapy the consequences, medical social and psychological, of a misinterpretation of such a clinical picture could be serious enough nowadays the need for exact diagnosis as a guide to treatment is more than ever important

CASE HISTORIES

Case XV Miss P, 882/1946, aged 15, was admitted to hospital complaining

bed for some months

On physical examination no abnormalities were found Nothing of note was revealed by an examination of the faeces There was no rise in the temperature The erythrocyte sedimentation rate was normal The blood picture was normal The tuberculin test (VON PIRQUET) was positive Chest X-ray and straight X-ray of the abdomen did not reveal any changes Nor did we observe anything of note from a gynaecological point of view

Suspecting tuberculous peritonitis, we performed an aspiration liver biop

> subchronic portal tubercles belonging to type II, with some giant cells There was no trace of necrosis In the parenchyma there were two young subtubercles of types III and IV No acid-fast rods were observed in the specimens, which were stained according to HALLBERG *Conclusion* non-caseating submiliary tubercles and subtubercles"

This finding rendered the diagnosis of tuberculous peritonitis extremely probable The patient was advised strict bed rest and good nutrition She returned at regular intervals for further examination At that time treatment with streptomycin was not possible

Just over a year later the patient had a slight rise of temperature, and the region of the caecum was found to be a little painful on pressure Some local resistance was felt The gynaecologist arrived at the diagnosis of tuberculous salpingitis Some months later the patient was admitted once more (to the gynaecological ward this time) because she had become much worse A guinea-pig inoculated with cervical secretion developed a positive tuberculin reaction and swelling of the lymph nodes two months later Tubercle bacilli were cultured from the lymph nodes

Case XVI Miss D aged 46, who had suffered from asthma for many years was admitted with vague abdominal pains

On physical examination there were no significant findings apart from

found The question arose whether they were in fact of a malignant

character and in order to obtain some measure of certainty we decided to perform an aspiration liver biopsy The histopathological examination of the biopsy material revealed two non-caseating tubercles of type I together with a subtubercle of type III and one of type IV In conjunction with the clinical findings the diagnosis of tuberculosis was now considered extremely probable

Artificial sunlight treatment cured the abdominal disease The seeming metastases, therefore, were probably tuberculous lymph nodes

On two occasions we have had the opportunity of examining an aspiration liver biopsy in patients suffering from chronic intestinal obstruction In both cases an extensive intestinal resection was performed and several old stenoses were found Microscopical examination of the stenotic areas pointed to granulomatosis but the result of examination of the liver tissue by serial section was negative The possibility of CROHN's disease in the two cases was seriously considered, although not proved In this latter disease we have had not enough opportunity of examining liver biopsies

CHAPTER X

TUBERCULOUS PERICARDITIS

In one of several cases of constrictive pericarditis we have found aspiration liver biopsy very helpful The biopsy was performed in order to gain an idea of the vascular state of the liver We found not only the expected serious degree of venous congestion, but also extensive haematogenous tuberculosis

CASE HISTORY

Ca e XVII Mr L 816/1949 aged 40 was admitted complaining of a feeling of persistent tiredness and listlessness and also of a painful sense of pressure in the region of the stomach About one month after the onset of symptoms the patient became short of breath on exertion This dyspnoea assumed such proportions that his removal to hospital became necessary

On physical examination the heart beat could not be felt The heart was somewhat enlarged towards the right at the cardiac apex and over the pulmonary artery the second sound was reduplicated on expiration We also found a greatly enlarged fairly firm pulsating liver There was a very distinct pulsus paradoxus and oedema of the legs There was no rise in temperature the erythrocyte sedimentation rate was 1 mm during the first hour and 2 mm during the second hour The blood picture revealed slight polycythaemia and there were no toxic changes in the leucocytes The urine showed only a distinctly positive urobilinogen reaction The tuberculin test (VON PIRQUET) was positive

On fluoroscopic examination of the chest pulsation of the heart was seen to be strikingly deficient movement to the left was very slight The radiologist thought he was faced with a case of constrictive pericarditis The lungs were normal

In order to establish the degree of stasis objectively an aspiration liver biopsy was performed We were very surprised by the histological findings The pathological report read as follows

The biopsy measured 1 3 cm long and was examined in serial section 128 sections were stained with haematoxylin-eosin and 44 according to HALLBERG No acid fast rods were observed In total 14 tubercles

were found, viz 4 belonging to type O, 5 to type I, 3 to type II, 1 · type III, and 1 to type IV The tubercles of types O and I were olde with caseating centres Apart from them an occasional fairly recen caseous tubercle was seen There was well-marked centrilobular congestion with considerable haemorrhage The wall of the central veins was not thickened "

In view of these findings it was decided to postpone operation on the constrictive pericarditis, in order to treat the patient first with streptomycin and P A S

What does this case teach us? In the first place it is of paramount importance to establish as carefully as possible the cause of the constrictive pericarditis before proceeding to pericardiolysis There is no consensus of opinion with regard to the frequency of a tuberculous aetiology, and we believe it is necessary either to exclude or to establish that aetiology as accurately as possible in every case In the above mentioned case the liver biopsy was of great help in this respect

In the second place it is very important to determine the degree of activity of the process underlying the constrictive pericarditis It is instructive to note that in our patient ordinary criteria failed to yield a satisfactory picture of the activity of the process and that liver biopsy revealed a very intensive dissemination Although ultimately the patient's general condition must remain the chief factor in assessing the need for pericardiolysis, yet knowledge of the activity of the process will influence the choice of the optimum time for operation; for the possibility of the surgeon cutting into areas of active tuberculosis with caseation is by no means negligible The possibility of consequent haematogenous dissemination, followed by a fresh localization of the process (for example, in the meninges) may be avoided if sufficient attention is paid beforehand to the need for ascertaining the activity of the process Serious mischief may be avoided by means of streptomycin, combined with other drugs, administered prophylactically before and after the operation If the process is very active, and if an operation cannot be postponed by means for instance of dehydration

therapy one will certainly have recourse to it in order to ‹
nish the possibility of post-operative complications

In the third place aspiration liver biopsy teaches us that
culosis of the pericardium like that of the pleura and the ·
neum may constitute part of a more general process In m
tis we mostly have to do with one or more active foc
cortex of the brain which unceasingly pour tubercl
into the cerebrospinal fluid and must be considered re:
for the symptoms of the disease It is quite possible that
pathogenesis exists in the tuberculosis of the pleura
peritoneum and even of the pericardium

The case history we have just related exemplifie
that aspiration liver biopsy may be helpful in all the
we have mentioned

CHAPTER XI

PULMONARY TUBERCULOSIS

Aspiration liver biopsy was originally performed in 15 cases of cavitating tuberculosis of the lungs, mainly for scientific reasons In fourteen cases we found the tubercles of the types I to IV mentioned at the beginning of this monograph This observation formed the starting point of a comprehensive general study of pulmonary tuberculosis, which has taught us that this disease (especially with regard to its early diagnosis) is one of the principal indications for liver biopsy Apart from the primary complex, which has already been discussed, we afterwards investigated other forms of pulmonary tuberculosis with the aid of liver biopsy Out of *30 patients with infiltrations, ranging from* very small to relatively large, seen in the chest X-ray, 28 proved to have tubercles in the liver In most cases serial sections of the liver biopsies proved indispensable, for it was especially in the cases of *so-called minimal tuberculosis* that we *sometimes* observed young and small subtubercles of type IV unaccompanied by larger lesions The patients were seemingly healthy soldiers, in whom a routine X-ray examination revealed one or more small areas of infiltration In several cases the temperature and the erythrocyte sedimentation rate were normal, and in some tubercle bacilli were cultured afterwards from the stomach washings

CASE HISTORY

Case XI III Mr H aged 20 was admitted to a military hospital in March 1949 because slight changes had been found in his chest X-ray The temperature was normal The erythrocyte sedimentation rate was 14 mm

during the first hour The tuberculin reaction was positive in the sputum no tubercle bacilli could be found

On April 14th 1949 a liver biopsy was performed The pathological report read as follows

The biopsy measured 2 7 cm long and was examined in serial section (172 sections) Twelve relatively young lesions of type IV were observed in the parenchyma

Conclusion twelve young subtubercles of type IV suspicious of tuberculosis Follow up of this patient is essential

Six months later it was learned that guinea pig inoculation with fasting gastric contents was positive

On the one hand the clinical and radiological pictures and the biopsy findings on the other did not always run parallel Sometimes the degree of dissemination seen in the liver proved to be much more serious than had been anticipated while at others only a few small subtubercles were to be seen It is obvious that pulmonary tuberculosis is no exception to the general rule that haematogenous dissemination to other parts of the body is frequent with all active local lesions but the factors that determine the occurrence and degree of this dissemination remain obscure Immunological considerations must be important but the nature of immunity in tuberculosis remains a disputed subject which lies outside the scope of this monograph

We need hardly explain that aspiration liver biopsy will seldom be resorted to in cases of phthisis with cavitation when tubercle bacilli can be demonstrated in the sputum Yet there may be circumstances which render this operation advisable as may be seen in the following case

CASE HISTORY

Case XIX Mrs B D 645/1948 aged 9 was admitted because of a high temperature following delivery Her previous history included an attack of right-sided pleurisy six years earlier and two years after that episode a three months rest-cure

On physical examination the liver and the spleen were just palpable The erythrocyte sedimentation rate was 68 mm during the first hour and 107 mm during the second hour The blood picture showed unmistakable toxic changes the urine was normal Chest X ray showed bilateral

tuberculosis of the lungs with a cavity near the left hilus The sputum contained many acid-fast rods which on culture were confirmed as tubercle bacilli

In order to acquire an idea of the extent and the activity of the process an aspiration liver biopsy was performed The pathological report read as follows

"The biopsy measured 2 1 cm long and was examined in serial section (112 sections) We observed 77 minute tubercles, only 2 of which were of type II, 27 belonging to type III, and 48 to type IV Only 3 were attached to a portal tract, the remaining 74 being entirely situated *in* the parenchyma Three foci are of a very young large-cellular type two are old with long narrow nuclei the remaining 72 are of a young type, though often an intermediate age is suggested by the nuclei of the epithelioid cells Giant cells are lacking Necrosis is nowhere to be seen, and in only one focus is there a trace of fibrin Eosinophil leucocytes are not observed in contrast to neutrophils *Conclusion* very extensive haematogenous dissemination in the form of subtubercles in the parenchyma and a few submiliary tubercles"

As a result of this finding, taken with the patient's serious febrile condition it was decided to treat her with streptomycin About six weeks after th commencement of this therapy another liver biopsy was performed The pathological report on the liver tissue read as follows

"The biopsy measured 2 cm long and was examined in serial section (136 sections) The difference from the first biopsy is striking In total only 8 foci are observed 2 of which are of type II, 3 of type III and 3 of type IV Both type II tubercles are portal one of them containing a giant cell of LANGHANS The 6 subtubercles lie in the parenchyma In only one are the epithelioid cell nuclei young in

tration

The cavity in the left lung together with the enlarged lymph nodes in the mediastinum must be looked upon as the origin of the haematogenous dissemination It goes without saying that treatment of this focus was of first importance After the temperature had been normal for some weeks pneumothorax was decided on Apart from some cord-like adhesions in the apical region a complete collapse of the lung was effected The cords were severed by cautery according to the method of JACOBAEUS

When antibacterial treatment had been given for three months a third biopsy was performed before the patient was discharged The pathological report on the liver tissue read as follows

'The biopsy measured 1.5 cm long and was examined in serial section (108 sections). Only six small foci were observed, all of them

infiltration.

Conclusion: remnants of an earlier haematogenous dissemination in the parenchyma. Moderate fatty change.

The patient went home in good condition. The pneumothorax was maintained as an outpatient. She is at present in excellent health.

In addition to the local process in the lung, there was in this case an extensive haematogenous dissemination accompanied by high fever. By means of aspiration liver biopsy the presence of one form of dissemination (viz. that to the liver) was objectively proved, and this observation in combination with the clinical symptoms led to the administration of streptomycin. Successive liver biopsies then demonstrated that, apart from the collapse therapy and general rest, streptomycin favourably influenced the course of the disease. Aspiration liver biopsy is, however, comparatively rarely indicated in cases of cavitating tuberculosis of the lungs, depending on a full review of the clinical symptoms and the X-rays of the chest.

CHAPTER XII

TUBERCULOSIS OF THE LYMPH NODES

Before considering the more important subject of mediastinal lymph node tuberculosis, we wish to discuss involvement of the *superficially situated nodes* We have performed aspiration liver biopsy in seven such cases, and in all these cases tubercles were found in the liver tissue It goes without saying that in these cases liver biopsy is rarely necessary, for biopsy of a lymph node carries with it even less risk for the patient while it confirms or excludes the clinically probable diagnosis equally if not more clearly, and with less trouble Nevertheless we have performed aspiration liver biopsy in such cases on a few occasions, at first only for scientific reasons Experience has taught us that at times this seemingly benign form of tuberculosis is in reality anything but innocent, and that in these cases the lymph nodes are not the only site of the tuberculous process, there may be clinically silent but microscopically active foci elsewhere in the body

When one knows this, it will be clear one should aim, in designing treatment at avoiding every trace of the conception that these cases are comparatively unimportant It is obvious that when tubercles in the liver are especially numerous or especially young in type, the treatment must be correspondingly thorough Personally we believe that every case of active tuberculosis carries a tendency to haematogenous dissemination, our findings with aspiration liver biopsy prove this irrefutably We therefore arrive at the conclusion that every case of active tuberculosis should be treated with meticulous care, irrespective of the results of the pathological examination of the liver One may ask whether in such cases, apart from scientific interest,

there is also a practical indication for liver biopsy This question must be answered in the affirmative We are of the opinion that aspiration liver biopsy is indicated in those forms of tuberculosis of the superficial lymph nodes where fever or a sub febrile temperature or a chronic sinus is present It need hardly be said that enlargement of the spleen reinforces this indication, for the clinician knows that the enlargement of the spleen may be an expression of haematogenous dissemination

CASE HISTORY

Case XX Mrs v d W -d R 499/1948 aged 57 was admitted for treatment of a colloid goitre She also complained of nervousness insomnia and a distended feeling in the abdomen On physical examination a large rounded firm goitre was found In the neck the scars of several sinuses could be seen There were enlarged lymph nodes in the right axilla and behind the left ear No further abnormalities were found The erythrocyte sedimentation rate was 13 mm during the first hour and 34 mm during the second hour The blood picture was normal The urine was normal The tuberculin test (VON PIRQUET) was positive The temperature fluctuated between 37 5° and 38 9° C The chest X ray revealed some fibrosis of the upper part of the right lung

The enlarged lymph node in the right axilla was punctured and caseous material was found. No acid fast bacilli were seen on microscopical examination Pus aspirated from the mass behind the left ear was proved to contain tubercle bacilli of human type

In view of the raised temperature and the tuberculosis of the lymph nodes haematogenous dissemination of the process was considered probable In order to confirm this suspicion and also in order to get an idea of the extent of the process we performed aspiration liver biopsy The pathological report read as follows

The biopsy consisted of six portions measuring together ½ cm long They were examined in serial section In total 48 sections were stained with haematoxylin-eosin and 48 according to HALLBERG Twenty seven tubercles were found viz 3 of type I 9 of type II 8 of type III and 7 of type IV They are recent with many neutrophils and a sporadic eosinophil No necrosis is seen In one tubercle there is a trace of fibrin Some giant cells of the foreign body osteoclastoma and LANGHANS types are observed Five tubercles are certainly portal In spite of a meticulous search no acid fast rods were found.

Conclusion extensive recent haematogenous dissemination

It goes without saying that thyroidectomy was postponed for the time being, and the patient was advised to observe strict bed rest, with good nutrition and extra vitamins We lost all trace of her

We will now consider the clinical importance of aspiration liver biopsy in cases with *enlarged lymph nodes in the lung hili and the mediastinum* First and foremost it has become clear that this type of examination is a valuable contribution to the differential diagnosis in such cases Generally speaking, the differential diagnosis of hilar and mediastinal lymph node enlargement is a clinical one, but in many cases the clinician cannot distinguish HODGKIN's disease, tuberculosis, sarcoidosis, lung tumour, etc Although in some cases the chest X-ray is more or less characteristic of one of these diseases, this is by no means always true, and tomographic examination also often fails to supply the diagnosis

Aspiration liver biopsy was performed in 74 cases of enlargement of lymph nodes in mediastinum and lung hilus, all of which were on clinical grounds possibly or probably cases of tuberculosis or sarcoidosis Haematogenous dissemination was in this way established in 71 of the cases We shall not discuss here the changes in the liver in sarcoidosis, and its place in the differential diagnosis of tuberculosis It is beyond doubt that a positive liver biopsy is extremely valuable in arriving at the diagnosis in these cases

As yet it is impossible to say how important a negative serial-sectioned liver biopsy is in these cases We believe, however, that such a finding taken in conjunction with the clinical symptoms, always deserves close attention, and that it renders the diagnosis of tuberculosis or sarcoidosis less probable In one patient with enlarged hilar glands, with the clinical diagnosis of probable tuberculosis, but with no tubercles in the liver biopsy, it was afterwards found that the true diagnosis was HODGKIN's disease

In rare cases the tubercles in the liver may occur simultaneously with some other pathologic process in the enlarged lymph nodes

of lung hilus and mediastinum — carcinoma for example or HODGKIN's disease We have not yet observed any such examples of multiple pathology and we believe that they must be very unusual and they do not affect the results of this investigation Aspiration liver biopsy may also assist in cases where the differential diagnosis between tuberculosis and primary bronchial carcinoma causes difficulty The diagnosis of bronchial carcinoma was considered very probable in two cases In one of these the surgeon was about to perform an exploratory thoracotomy aspiration liver biopsy revealed tuberculosis just in time That the therapy based on this diagnosis was successful goes without saying In the second case the shadows found in the chest X-ray were reported as metastases with the aid of an aspiration liver biopsy however the diagnosis of tuberculosis was established with all its therapeutic and prognostic consequences We do not propose in this monograph to enter into the value of sputum cytology in the diagnosis of primary bronchial carcinoma for it has been well described by WOOLNER and MCDONALD We only wish to draw attention to the great value of aspiration liver biopsy in some obscure cases of tuberculosis

In this connection it would seem useful to consider some of the disadvantages from the clinical point of view of the available methods of bacteriological study of tuberculosis — that is to say of course in cases where direct examination of smears does not give the answer at once In the first place (and certainly when a successful treatment depends on an early diagnosis) the long duration of the examination (in most cases at least six weeks) is an almost insuperable objection Moreover a negative result does not exclude tuberculosis In the two cases mentioned above which elsewhere were taken for bronchial carcinoma the bacteriologist was unable to demonstrate tubercle bacilli Both patients then came to our clinic and it was the aspiration liver biopsy which gave the right diagnosis

In the cases of tuberculosis of the lymph nodes it is again possible to see how exceedingly frequent is haematogenous

become active Elsewhere in the body, too, (e g in the brain) these clinically latent foci may suddenly flare up and give rise to a fresh *manifestation of the process* At the end of this chapter we shall briefly describe a case where renal tuberculosis was found accidentally during microscopical examination of the kidney tissue, although there were no clinical symptoms Subsequent liver biopsy also revealed tubercles In this case the *tuberculosis was entirely latent*

It is therefore, of the greatest importance that patients with so-called unilateral tuberculosis of the kidney (whether or no surgical intervention is necessary) should undergo prolonged treatment with the modern anti-tuberculous drugs, P A S , etc Treatment must be protracted because, generally speaking, it is a long time before a clinical improvement is followed by histological inactivity This was brought home to us very convincingly in studying disease elsewhere On several occasions it was possible to speak of a clinical recovery, while serial examination of the liver tissue revealed new-formed tubercles We cannot point to actual cases of renal tuberculosis in which this has happened, but it is most unlikely that this site constitutes an exception

Sometimes it is not easy to arrive at the diagnosis of tuberculosis of the kidney In such difficult cases the liver biopsy may be of assistance, and as a general rule we would limit the indication for the operation to such cases

CASE HISTORIES

Case XXII Mr R 366/1947 aged 23 was admitted complaining of continual pains in the left upper part of the abdomen On physical examination nothing was found The erythrocyte sedimentation rate however was constantly raised to a considerable degree viz 115 mm during the first hour and 128 mm during the second hour The blood picture did not reveal anything of note The tuberculin test (VON PIRQUET) was positive Leucocytes were regularly seen in the urinary sediment On systematic radiological examination, intravenous pyelography of the left kidney revealed a constant defect Repeated bacteriological search for tubercle bacilli in the urine was fruitless As a tumour of the kidney was suspected

we decided to perform an exploratory laparotomy, it did not reveal anything abnormal however

> tissue of both organs The liver biopsy measured 1 5 cm long and the kidney biopsy 1 3 cm In total there were 96 sections which were serially examined In the liver parenchyma were found in total 3 small foci 1 of them belonging to type III and 2 to type IV The kidney biopsy showed no lesions
>
> *Conclusion* three subtubercles in the liver parenchyma, which may very well be of tuberculous origin"

Hence the diagnosis of renal tuberculosis became more probable Bacteriological examination of the urine for tubercle bacilli was resumed, one of the cultures became positive after three months thus confirming the diagnosis of tuberculosis

The patient was advised to undergo an operation under the protection of streptomycin and P A S

Case XVIII Mrs M-C 501/1949 aged 48 was admitted complaining of headaches from which she had suffered for a considerable time She was also troubled by tinnitus dizziness and seeing stars Her troubles were mainly the effects of hypertension On physical examination a slight dilatation of the heart to the left was observed The blood pressure was 210/120 mm Hg There were no abnormalities in the urine The erythrocyte sedimentation rate was 9 mm during the first hour and 28 mm during the second hour The blood picture showed no irregularities The tuberculin test (VON PIRQUET) was positive

It was decided to perform sympathectomy In the course of the operation biopsy of the left kidney was done The pathological report by Dr W E F WINCKEL states that apart from the arteriosclerosis and arteriolosclerosis a fairly recent non-caseating conglomerate tubercle of type O/I was found unexpectedly in the cortex In order to obtain an impression of the extent and the activity of the process we performed an aspiration liver biopsy The report read as follows

> The biopsy measured 2 4 cm long and was examined in serial section (92 sections) In the parenchyma 73 lesions were found 12 of them belonging to type III and 61 to type IV This is a relatively recent dissemination for apart from the lymphocytes a few neutrophils are still observed between the epithelioid cells
>
> *Conclusion* extensive relatively recent haematogenous dissemination'

The patient was treated with strict bed rest and P A S

CHAPTER XIV

TUBERCULOSIS OF THE ADRENALS

Aspiration liver biopsy was performed in one case of ADDISON's disease As is well-known, this disease is generally speaking tuberculous but it is equally a well-known fact that primary adrenal atrophy, metastatic carcinoma pituitary disease or amyloidosis *may also give rise to the same clinical syndrome* (incidence of non-tuberculous ADDISON's disease WELLS 10%, GUTTMAN 20%)

In this connection the report of RICKARDS and BARRETT acquires a *special significance* The authors describe an example of ADDISON's disease which is characterized by the presence of non-caseating granulomata with giant cells Formerly such cases were regarded as examples of a glandular disease due to non-caseating tuberculosis, but study of these cases leaves little doubt that they represent examples of the disease "giant cell granuloma", considered by these authors to be a specific clinico-pathological entity

In general the significance of aspiration liver biopsy in cases of ADDISON's disease is twofold In the first place the tuberculous genesis can be established, and in the second place it is possible in this way to make a diagnosis of general haematogenous tuberculosis We need hardly explain that the view of the haematogenous origin of adrenal tuberculosis may be corroborated in this way It goes without saying that a patient suspected of this disease, has to be observed attentively after the puncture, in view of the greater liability to shock in these cases This can not be regarded, however, as an absolute contra-indication to aspiration liver biopsy

CASE HISTORY

Case XVII Mr E 723/1949 aged 48 was admitted to the hospital complaining of extreme fatigue The patient had also observed that he had developed generalized bodily pigmentation At the age of eight he had suffered from pleurisy with effusion and when he was twenty five there was a slight relapse of this About the same time he had a cold abscess of the left buttock

The present complaint led the local physician to a diagnosis of ADDISON s disease When the patient was admitted to hospital in Leyden for observation he was placed on DOCA intramuscularly daily These injections were continued in our clinic

On physical examination nothing significant was found apart from skin pigmentation There was no pigmentation of the buccal mucous membrane The blood pressure was 130/80 mm Hg The erythrocyte sedimentation rate was 11 mm during the first hour and 24 mm during the second hour Haematological investigation showed only leukopenia The tuberculin test (VON PIRQUET) was positive There was no fever

The chest X ray revealed numerous small blurred shadows there was no question however of definite tuberculosis of the lungs

In vi

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aspirati

> The biopsy measured 7 6 cm long and was examined in serial section (110 sections) In total 49 tubercles were observed 3 of them of type I 12 of type II 6 of type III and 28 of type IV It is found that three different disseminations can be distinguished with certainty a fresh dissemination with mitoses and many eosinophils an older so-called large cell hyperplasia and a still older one showing the commencement of scarring In some of the lesions of type III and several of type IV the cells have phagocytosed many black pigment particles These give a negative reaction for iron In one of the giant cells a so called asteroid body was found
>
> *Conclusion* extensive non-caseating chiefly large-cell epithelioid cell granulomatosis (tuberculosis) three separate disseminations of different ages Anthracosis

In view of the result of this examination it was advised that specific antibacterial therapy be added to the hormonal treatment About a year after his admission to hospital he died of a myocardial infarction at home

CHAPTER XV

BONE AND JOINT TUBERCULOSIS

Aspiration liver biopsy was performed in seven cases of tuberculosis of the skeletal system and joints In six cases tubercles were observed in the liver

Here again, it may be asked what are the indications for liver biopsy Every clinician knows only too well that even in the presence of radiological bone changes the diagnosis of tuberculosis may be uncertain Lesions of this type are often inaccessible to ordinary biopsy (which is in any case not devoid of risk) The position is worse when the presence of a lesion is suspected on clinical grounds in the absence of X-ray changes This holds especially for early tuberculous arthritis Formerly a presumptive diagnosis on clinical grounds might have been adequate, but now the clinician requires a greater measure of certainty before deploying his full therapeutic armamentarium Correct and prompt treatment in the early stages may now completely prevent irreversible changes in the joints By the time X-ray changes are present the prognosis has become more doubtful, although even at this stage it is better than formerly Aspiration liver biopsy may assist considerably in arriving at an early diagnosis and may be the only available means of establishing it with certainty

Here again the considerations which we mentioned in discussing miliary tuberculosis apply, with the exception perhaps of those related to lumbar puncture It is clear that it is impossible to examine regularly the spinal fluid of all the patients in whose liver tubercles have been observed, although on theoretical grounds it would be easy to defend such a course Here, too the clinical status of the case must be the deciding factor

It is a well-known fact that operative manipulation of a tuberculous joint may disseminate the bacilli It is even probable that normal movement of the inflamed joint may cause dissemination, so that liver biopsy may be expected to be positive in a large percentage of cases This operation may therefore prove a most welcome diagnostic method in affections of the skeletal system or the joints where the aetiology is obscure

CASE HISTORIES

Case XXV Mr S R 476/1948 aged 50 had suffered from pain in the right knee for six years It was said to have commenced after injury For five years he had received various forms of physiotherapy In January 1948 at the health centre for rheumatic diseases the possibility of tuberculosis was raised Immobilization of the joint had no effect Finally an open biopsy of the capsule of the knee joint was performed but no histological evidence of tuberculosis was found Subsequently a consultant physician treated the patient with gold and amidopyrine there was no improvement

On clinical examination the circumference of the right knee was found to be 25 mm more than that of the left knee A flexion contracture was present The erythrocyte sedimentation rate was 12 mm during the first hour and 30 mm during the second hour The tuberculin test (VON PIRQUET) was positive

The chest X-ray showed nothing of note apart from some old opacities Yet tuberculosis was not ruled out especially in view of the X-ray appearances of the joint in the lower part of the femur there were some ill-defined radiolucent areas associated with distinct periosteal irregularities and thickenings Another synovial biopsy was done The diagnosis was focal cellular proliferative inflammation with tubercles and necrosis The pathologist (Dr G J VERDONK) considered however that he could not altogether exclude the possibility of a rheumatic process

After the biopsy the patient developed fever An aspiration biopsy of the liver was then performed The pathological report read as follows

> The biopsy measured 3 cm long and was examined in serial section (108 sections) In total 47 tubercles were observed 3 of them of type II 11 of type III and 33 of type IV In addition to lymphocytes and polymorphs the tubercles of type II also contain some eosinophils and one contains some fibrin and 3 giant cells Staining according to HALLBERG is negative All the foci are situated in the parenchyma and they are of a young type Some KUPFFER cells contain a grayish brown pigment such as is seen in patients treated with gold

Conclusion many recent tubercles, one of which contains giant cells Highly suspicious of tuberculosis"

Meanwhile tubercle bacilli had been cultured from the synovial fluid, *thus establishing a diagnosis of tuberculous arthritis with haematogenous dissemination*

Therapy consisted of surgical resection of the joint, combined with treatment with streptomycin and P A S At the operation three bone foci were found in the proximal part of the tibia Abscesses in the popliteal fossa were also observed After pathological examination of the resected knee Dr. G J VERDONK reported that it showed extensive caseating tuberculosis

Six months after resection, when the plaster of Paris was removed, the patient's condition was satisfactory, although the sedimentation rate was still high (23 mm during the first hour and 41 mm during the second hour)

Case XXVI Miss O , 946/1949, aged 23, was admitted with intense pain in the left hip, which had appeared acutely and was attended with fever

On physical examination the only finding was limitation of all movements of the left hip joint The erythrocyte sedimentation rate was 63 mm during the first hour, and 100 mm during the second hour The blood picture showed only slight leucocytosis The urine was normal The chest X-ray revealed nothing of note X-rays of the hip joints were normal The diagnosis of tuberculosis was however seriously considered partly owing to the fact that 2½ years previously the patient had suffered from tuberculous pleurisy

In order to confirm the diagnosis of tuberculosis an aspiration liver biopsy was performed The pathological report read as follows

"The biopsy measured 2 7 cm long, and was examined in serial [illegible] foci were observed, one of which [illegible] miliary [illegible] ing of fibroblasts, co[illegible] with some serous exudate Of the four foci in the par[illegible] of type III, and two of type IV One focus of type III is still young and contains a mitosis, the other foci are of intermediate age The parenchyma is normal

Conclusion one young submiliary portal tubercle, and four subtubercles in the parenchyma Tuberculosis is very probable"

The patient was treated with streptomycin and P A S combined with rest, good nutrition, and immobilization of the left hip joint Nineteen days after the commencement of this therapy the sedimentation rate had dropped

to 10 mm during the first hour, and 25 mm during the second hour Within one week the temperature became normal, and remained so until the patient was discharged five and a half months after admission

Before she was discharged a second aspiration liver biopsy was performed The report read as follows

> "The biopsy measured 2 cm long and was examined in serial section (120 sections) Only 8 pericentral lesions of type IV were found, partly of a rather young type, and partly of an intermediate type No mitoses were observed
>
> *Conclusion* Eight subtubercles of type IV"

The patient was advised to continue the rest cure at home, combined with P A S and extra vitamins Immobilization of the hip joint was continued

Four months afterwards the patient was again admitted for a follow-up examination She was in a very good condition, the function of the hip joint was 100% After discussion with the surgeon careful movement of the hip was begun She was advised to take much rest at home, and to continue the P A S therapy

The patient is now in excellent condition On physical examination nothing significant can be found The erythrocyte sedimentation rate is normal She consulted her family physician in connection with sterility, bacteriological examination of the menstrual blood revealed the presence of tubercle bacilli

CHAPTER XVI

TUBERCULOSIS OF THE EYE

In fourteen cases of eye disease in which the aetiology was not clear (11 cases of iridocyclitis 2 cases of keratitis and 1 case of retinitis) we had recourse to aspiration liver biopsy In each of these cases it was suspected that the disease of the eye might be a manifestation of tuberculosis Experience has taught the oculist that such intra-ocular processes have often a tuberculous origin, and therapy must conform to these ideas The therapeutic consequences being far-reaching it is most desirable (as in most cases when considering therapy) to be as sure as possible of the aetiology

In eleven out of the fourteen cases tubercles were observed *in serial sections of the liver biopsy in eight of the cases they* were exclusively of the types III and IV

CASE HISTORIES

Case XXIII Mr H 504/1950 aged 27 visited our outpatient department with general vague complaints and was found also to be suffering from a chronic iridocyclitis in both eyes

On physical examination there was nothing of note The X-ray of the chest showed a distinct spotty shadowing with enlarged hilar lymph nodes The tuberculin test (VON PIRQUET) was negative the MANTOUX was positive at 1 10 000 The red cell sedimentation rate was 9 mm during the first hour

The diagnosis of sarcoidosis was considered but could not be established The chest X ray was very suggestive of this disease though the positive MANTOUX spoke against it

A liver biopsy was performed elsewhere Apart from one subtubercle of type IV nothing abnormal could be found but the biopsy was far too small for satisfactory study

In view of the chronic iridocyclitis the patient was treated with tuberculin

and P A S , treatment being continued elsewhere On one occasion tubercle bacilli were cultured from the sputum

About 3 years later the patient returned to our department The iridocyclitis was now much worse To determine the activity of the process a second liver biopsy was performed The pathological report read as follows

"The biopsy measured 1,2 cm long and was examined in serial section, [illegible]

tubercles of type O and I with sometimes small hyaline bands Two of the 8 tubercles of type II were completely scarred, but on examination in serial section one was found to contain a giant cell and a few epithelioid cells Some of the remaining tubercles were rather young, a few eosinophil leucocytes were found in these Ten of the 28 subtubercles, all located in the parenchyma, belonged to type III, 18 to type IV Further there was found a slight fatty infiltration
Conclusion Many non-caseating partly young, partly older and partly sclerosed tubercles of all types"

The patient was treated with P A S streptomycin and I N H Six months later a third biopsy was performed The pathological report read as follows

"The biopsy measured 1,5 cm long and was examined in serial section (120 sections) In total 69 foci were observed 10 submiliary tubercles and 59 subtubercles, 58 of the latter belonged to type IV, 1 to type III Only a few were young The submiliary tubercles were located in the portal spaces and were markedly older than those in the former biopsy There were 6 conglomerate tubercles 1 of type O and 5 of type I built up of mainly large-cellular foci surrounded sometimes by broad hyaline bands One was somewhat younger the hyaline band was narrower and surrounded by a rather broad zone of lymphocytes plasma cells and eosinophil leucocytes Further there was one solitary tubercle of type I with a large-cellular structure and a periphery consisting of old connective tissue without hyaline One of the 3 tubercles of type II was relatively young and surrounded by a zone of lymphocytes one cicatrised with a centre of epithelioid cells and one a hyaline ball with a large-cellular centre The parenchyma showed some eosinophilic degeneration and dissociation of the individual liver cells with slight fatty infiltration
Conclusion Many non-caseating older and cicatrising tubercles and conglomerate tubercles of types O I and II and many subtubercles of type IV"

Unfortunately afterwards the patient was observed and treated elsewhere and we have lost all trace of him

Case XXVIII Miss P , 5559/1948, aged 47, was referred to us by the ophthalmological outpatient department for a general examination, as she was suffering from iridocyclitis

Physical examination showed nothing of significance except the iridocyclitis in the right eye Tuberculosis was frequent in the family The patient told us that from time to time she had small erythematous spots scattered all over her body The erythrocyte sedimentation rate was 14 mm during the first hour, and 30 mm during the second hour The blood picture was normal The MANTOUX reaction was positive The chest X-ray was normal

In order to establish the aetiology of the iridocyclitis it was decided to perform an aspiration liver biopsy The pathological report of the liver tissue read as follows

> "The biopsy measured 3 6 cm long and was examined in serial section (99 sections) Nine subtubercles were observed in the parenchyma, 2 of type III and 7 of type IV They are partly recent partly somewhat older
>
> *Conclusion* partly recent, partly somewhat older subtubercles of types III and IV, which are suspicious of tuberculosis"

The diagnosis of tuberculous iridocyclitis had now become probable The patient was advised rest, and P A S was prescribed

CHAPTER XVII

THE SIGNIFICANCE OF SUBTUBERCLES OF TYPES III AND IV

We turn now to discuss a phenomenon which has been mentioned many times in earlier chapters In the liver biopsies of patients known with certainty to be suffering from active tuberculosis we have regularly observed epithelioid-cell subtubercles of types III and IV The significance of these differs entirely from that of the better-known submiliary tubercles (usually portal) of types O, I, and II As a rule these epithelioid-cell subtubercles are situated in the parenchyma But sometimes they are located in the portal spaces and probably the majority of these have to be considered as preliminary stages of the submiliary tubercles of types II, I or O Occasionally parenchymal lesions of type III may be observed which have irregular boundaries and produce atrophy of the surrounding liver cells shown by the intense staining of the latter with eosin These probably must be considered as preliminary stages of the type II tubercles sometimes to be found in the parenchyma We have never yet observed tubercles of types I and O with a parenchymal location

However most of the parenchymal subtubercles of types III and IV are clearly outlined epithelioid-cell foci of round to oval shape They may be found in all sections of the lobule but show a preference to a pericentral location, which applies especially to the smallest type IV They are occasionally attached to the wall of the central vein more often to a hyperaemic capillary In young lesions mitoses neutrophils and or eosinophils with a few lymphocytes may be found When older lesions contain any cells these consist exclusively of a few lymphocytes These lesions never caseate they very rarely (in the case

of type III only) contain a giant cell Although the epithelioid cells do not develop into ordinary fibrocytes, their nucleus, which is at first vesicular and pale-staining, becomes in time longer, drawn out and pyknotic Subtubercles of these types never develop into true tubercles, but disappear completely without leaving a trace This statement is based on the examination in serial section of serial liver biopsies, i e repeated biopsies at intervals in each of a substantial number of cases These lesions in all probability arise from the KUPFFER cells In favour of this statement we should like to mention that the epithelioid cells of subtubercles of types III and IV occasionally contain some lipofuscin derived from destroyed liver cells

What is the clinical significance of these small granulomata (which we observed first in sarcoidosis) when they are found alone in liver biopsies performed for diagnostic purposes in persons suspected of tuberculosis? Before we could answer this the examination of a large series of controls was necessary Between 1946 and 1950 practically all liver biopsies done for other indications (approximately 150 cases) were examined in serial section We can conclude from these that the presence of subtubercles of types III and IV is not pathognomonic, but is always suspicious of tuberculosis or sarcoidosis We observed such lesions four times in *HODGKIN's disease* once in *infectious mononucleosis*, and once in *malaria* (The epithelioid cells of the type III and IV lesions in the last mentioned case contained malaria pigment, which supports the view that they may arise from KUPFFER cells) We are not in a position to decide how far in these cases they were a response to the agent of the disease, or a consequence of simultaneous tuberculosis At the autopsy (by Dr STRAUB) on one of the patients suffering from HODGKIN's disease however, not a trace of tuberculosis was found

We also had the opportunity of performing liver biopsy on a patient suffering from *brucellosis*, in which disease, on theoretical grounds we expected to find these lesions as well as the more classical tubercles observed by HOFFBAUER and SPINK They were present in large number The same observation

was made in the only case of *berylliosis* we have seen. Unfortunately we have no experience of their occurrence in *syphilis** and in *histoplasmosis, coccidiomycosis, blastomycosis, torulosis,* and various tropical diseases, in which we consider their appearance as possible. In a few cases of *infectious hepatitis* pericentrally located lesions of type IV were found. These were quite characteristic, for the epithelioid cells (= KUPFFER cells) are loaded with lipofuscin to a degree never seen in tuberculosis. Since in more severe cases the virus of infectious hepatitis by preference destroys pericentrally located liver cells, a good deal of lipofuscin may be liberated. This pigment is phagocytosed by KUPFFER cells and this leads to the formation of solitary lipofuscin-containing cells or to the formation of small clusters of such cells which we should like to call "lipofuscin granulomata".

Thrice we have had the opportunity to study the liver at autopsy in cases of *typhoid fever*, in two of these cases by means of aspiration biopsy directly postmortem. The common typhoid fever lesions differed from those seen in tuberculosis, sarcoidosis, brucellosis, beryllios is and HODGKIN's disease in the presence of an abundance of neutrophils. Moreover the nuclear lobes of these polymorphs had become separated, an observation which up to now we have made only in this disease.

In 10 cases, where the clinical symptoms were such that tuberculosis could not be excluded from the diagnosis, we found 1, 2 or as many as 5 subtubercles of type IV. In view of the circumstances that from time to time tuberculosis is present and heals without being noticed, we do not look upon these cases as speaking against our view. In a number of cases we made a diagnosis of "suspicious" or "very suspicious of tuberculosis", based exclusively on our finding of 1—20 fresh subtubercles of type III and/or IV, *together with the clinical symptoms.* This

* LAQUEUR and EGLI described miliary syphilomata observed in a liver biopsy without discussing the differential diagnosis from tuberculosis. In our opinion it is quite possible that these foci had a tuberculous aetiology. We have had the opportunity of discussing this paper with one of the authors (Dr LAQUEUR) who agreed with our views.

diagnosis was afterwards confirmed in 12 cases by the finding of tubercle bacilli in stomach washings, sputum, or urine Two of these cases have already been described in the sections dealing with renal tuberculosis, and pulmonary tuberculosis It is clear that the early therapy of such cases is very important In this connection we would recall the patient with post-partum fever, mentioned in the section dealing with tuberculosis of the lymph nodes The clinical symptoms, together with the subtubercles III and IV seen in the liver biopsy, decided us in favour of early streptomycin therapy This appeared to exert a decisive effect in the patient's subsequent complete recovery

In one case in which the presence of a mediastinal mass was the indication for liver biopsy we found a single subtubercle of type III in the otherwise normal liver Autopsy revealed mediastinal sarcoma, but there was also tuberculous pleurisy The clinical significance of these small foci should always be weighed in the light of the symptoms of the case under consideration It is certain that they may occur in abortive cases of tuberculosis

These small foci could only be regarded as specific for tuberculosis if they occurred exclusively in this disease, which is not the case It is also to be expected, if these are specific lesions, that it should be possible to demonstrate the tubercle bacillus in cases showing only these lesions (i e in the absence of tubercles of types O, I and II) not only histologically, but also on culture In the series reported in this monograph we have consistently failed to do this

We have attempted to approach this problem experimentally As the investigations lie outside the scope of this monograph, we will only mention our observation that it is not difficult, by means of intravenous injection of tubercle bacilli into the allantoic vessels of hen's eggs, to produce subtubercles of types III and IV as well as tubercles of types I and II, in the livers of chicks (technique of LEE and STAVITSKY) These subtubercles are loaded with acid-fast rods, and their appearances corroborate our view that they may be produced by tubercle bacilli In the chick liver they are even more easily overlooked than in the human liver

We have recently been able to prove that in man also these subtubercles may be caused by tubercle bacilli A baby born prematurely of a tuberculous mother died on the twenty sixth day from extensive bilateral caseating tuberculous broncho-pneumonia We expected on theoretical grounds that there would be subtubercles of types III and IV with acid-fast rods present in the liver and the spleen The conditions were most favourable a prematurely-born child practically without immunity dying from rapidly lethal tuberculosis of the lungs Our suspicions were confirmed and these lesions also proved so difficult to see — particularly in the spleen — that special experience proved necessary for their confident recognition In our opinion it is quite possible that in less abnormal circumstances these subtubercles may be the response to the phagocytosis and disintegration of a very small number of tubercle bacilli by and in the KUPFFER cells In this way failure to find any acid-fast rods becomes readily understandable *

We believe it would be wrong to assume that a tuberculous origin must be regarded as improbable because of the negative bacteriological findings in the subtubercles III and IV of our liver biopsies It was repeatedly observed by us that in advanced cases of tuberculosis with positive bacteriological findings in other material no tubercle bacilli could be demonstrated (either microscopically or culturally) in liver tissue containing tubercles of types I to IV inclusive In this connection we would point out that in fact tubercles of types O I and II are also not specific for tuberculosis They also occur in other diseases (e g sarcoidosis syphilis leprosy and other tropical diseases brucellosis beryllosis histoplasmosis and other fungus infections and talc granulomata) Even morphologically typical acid fast rods do not afford certainty Certainty is attained only when these acid fast rods have been proved to be tubercle bacilli by means of cultures or guinea-pig inoculation

* We subm[illegible]ed this op[illegible]n[illegible]n to our la[illegible]e [illegible] [illegible] professor of medicine [illegible] Leiden and he made the [illegible] appropriate [illegible] In that case the lesions [illegible] types III and IV will ha[illegible]e to be considered a[illegible] [illegible] [illegible]ubercl[illegible] ba[illegible]

It is the exception rather than the rule to be able to demonstrate acid-fast rods in liver tubercles even in cases of proved tuberculosis They are usually to be found in fresh caseating tubercles, but these are not often observed in the liver They are rare in old caseating tubercles (which are also of rare occurrence), and in the common epithelioid-cell tubercles This would tally with the fact that guinea-pig inoculation with liver tissue obtained by means of an *aspiration biopsy rarely yields positive results*

After completing this work we found that the German pathologists ORTH (1887), W FISCHER (1907) and B FISCHER (1910), and the French clinician DIEULAFOY (1901) pointed out half a century ago that the liver is not a favourable soil for the tubercle bacillus It is probable that the high resistance of this organ results from the presence of the KUPFFER cells This in our opinion, is the reason why macroscopically visible tuberculosis of the liver, and especially tuberculomata of the liver, are rare (WAGNER, ORTH, MORRIS, ASHTON) On the microscopic scale, however, our investigations go to show that tuberculosis of the liver is exceedingly frequent This also we found had already been pointed out more than half a century ago at autopsy by German pathologists (WAGNER, 1861, VIRCHOW, 1863, ORTH 1876, ARNOLD, 1880), and the French clinician DIEULAFOY (1901)

All this had, however, been largely forgotten in the course of time There seemed to be no descriptions of the common type III and IV subtubercles in medical literature Apparently they escaped the attention of all of us for all these years By careful examination we succeeded in finding these so-called subtubercles not only in liver biopsies but also at postmortem in the livers of patients dying of tuberculosis It may be wondered why they have been overlooked in autopsy material, *but the explanation* seems to be quite plain In the first place the portion of liver tissue removed at autopsy for microscopical investigation is relatively large and therefore one is more *likely to be satisfied* by the sight of one or more of the larger tubercles and the small foci escape attention But when a postmortem needle puncture is

performed and the small column of liver tissue obtained is examined in serial section practically no detail escapes the attention of the investigator and so even tiny foci may be observed A second reason for overlooking the subtubercles in the liver at autopsy is found in agonal and postmortal changes With loss of glycogen the mosaic pattern of the liver cells is replaced by a trabecular design and owing to this the foci lose their round or oval shape and become more drawn out and irregular The venous congestion of the liver and dissociation of the parenchyma which occur as postmortem changes also interfere with recognition of these small lesions

The only communication bearing on the subtubercles is one on liver puncture in miliary tuberculosis by JANBON et al in which a lesion of this type was illustrated These workers express the opinion that it represents a preliminary stage of the common submiliary tubercles Considering the evidence presented by our serial section examination of liver biopsies in 189 cases (in 25 of which the course of the disease was studied by serial biopsies) we cannot share this opinion Clear cut parenchymal foci of types III and IV do not develop into ordinary tubercles but disappear without leaving a trace

Continued clinical pathological experimental and statistical work is required to improve our insight into the significance of these small lesions

and bacteriology One is not in a position to evaluate the activity of a tuberculous process (especially in relation to the lesions seen in the liver in aspiration biopsies) when one has not a clear idea of the pathological background and the problems of immunity and bacteriology Although we cannot deny a certain parallelism in the concept of "activity" of the clinician and the pathologist, yet there is a distinct difference It is generally accepted that clinical activity always implies the presence of an active (in the pathologist's sense) tuberculous focus somewhere in the body, the reverse, however, is certainly not true Every experienced medical man knows of cases with no clinical evidence of active tuberculosis in whom autopsy has shown (as a secondary finding) active caseous foci containing virulent tubercle bacilli Many persons go much further still and hold, on good grounds, the view that every man with a positive tuberculin reaction harbours such a focus, "using" this focus to keep his immunity at the proper level Generally speaking we may say that the specific immune state derived from contact with virulent tubercle bacilli tends to check the development of the bacillus in the body A positive tuberculin test indicates that there are immune bodies present Perhaps it is too bold to suggest that absence of tubercles in liver biopsies in persons with a positive VON PIRQUET or MANTOUX reaction points to an equilibrium of the active focus and the production of immune bodies When this equilibrium is disturbed (the production of immune bodies decreasing, or the activity of the focus increasing) dissemination becomes possible In this way histological examination by means of serial sections of the aspiration liver biopsy might serve as a rough indicator of the degree of immunity (tuberculogram) Nevertheless it is well-established that in tuberculous meningitis the number of foci in the liver may be trifling, but the gravity of the clinical picture is determined independently by the state of the cerebral focus which affects the cerebrospinal fluid Hence local conditions may also decisively affect the course of the illness

It may therefore also be postulated that everyone who comes

into contact with tubercle bacilli passes through a phase of dissemination, equilibrium is in the great majority of cases soon re-established in favour of the host and the tuberculin test becomes positive From this point of view it must be regarded as probable that every primary infection is attended with dissemination of tubercle bacilli — which as a matter of fact we were able to demonstrate in two cases In short when one has noted the clinical facts it is possible to accept the view that every active tuberculous process involves dissemination That the liver can be made to serve as an indicator of the degree of this dissemination is an important fact because we may be able to use it as a reliable measuring rod or standard

Alternative techniques Theoretically the *spleen* could also be used for this purpose The fact that the liver is more accessible and less vascular however renders it technically more suitable for aspiration biopsy than the spleen Moreover aspiration spleen biopsy should in our opinion only be permitted under the control of the laparoscope (HAEX DEN OUDSTEN and VAN BEEK) To this must be added the fact that the above-mentioned tubercles (especially the smaller types) are more easily observed against the background of liver cells than against the more complicated splenic pattern In a few cases of miliary tuberculosis SCHLEICHER performed *sternal puncture* The tiny bone marrow particles were embedded in paraffin and examined in serial section In agreement with the investigations of RANDERATH tubercles were found in all cases (See also the important work of GERTRUD PEASE) Since aspiration biopsy of the liver provides us with a solid column of liver tissue we believe this method more satisfactory for diagnostic purposes

It has more than once been mentioned in medical literature that *tonsil* biopsy (suggested as a diagnostic operation in sarcoidosis by SCHAUMANN) might also be valuable in the diagnosis of tuberculosis Without discussing this question in detail it may be said that in our opinion a tonsil biopsy is of little importance in this respect This opinion is based on microscopical

examination at two levels of 64 pairs of tonsils removed in children suffering from pulmonary or hilar lymph node tuberculosis This investigation was carried out by one of us (v B) in co-operation with Dr WARNS, director of the sanatorium at Katwijk aan Zee In 23 cases a few submiliary tubercles and/or subtubercles were found These tubercles were not diffusely disseminated as in the liver but confined to one or two areas The result of a tonsil biopsy is hence more or less a matter of chance This opinion is reinforced by the fact that of the 23 positive cases quoted above 7 only had bilateral lesions while in 16 only one tonsil was involved But we must of course stress that these tonsils were not examined in serial section, but at two levels each only

PATHOGENESIS OF TUBERCLES OF DIFFERENT TYPES

Let us now look a little more carefully into the pathogenesis and the histological picture of the various types of tubercles in the liver We conceive the liver as a filter We imagine that small particles in the blood (whether portal or hepatic) are held up as emboli in the sinusoids of the liver, the larger particles (conglomerates of tubercle bacilli or reticulo-endothelial elements from elsewhere which have phagocytosed tubercle bacilli) in the portal tracts and at the periphery of the lobule, the smaller particles (solitary tubercle bacilli), on the other hand, more towards the lobule centre KUPFFER cells are well known to phagocytose small particles One can therefore imagine that as far as the tubercle bacilli are concerned, *once they have entered the vessels of the liver they will be phagocytosed by these cells* We were able to observe this directly in the case of one patient who died of exceptionally acute tuberculous infection It is an obvious step to assume that these KUPFFER cells, having ingested the tubercle bacilli, thereafter act as starting-points for small tubercles This view finds support in an observation made by us in a patient suffering from anthracosis and pulmonary tuberculosis We found carbon not only in the KUPFFER cells but also in the subtubercles in the liver parenchyma (types III

and IV) We can only explain this by assuming that the proliferated cells of these granulomata have phagocytic properties

It is theoretically possible that the stimulus to formation of the subtubercles in the liver is not the direct presence of bacilli but the effect of toxins This view is not supported however by the strictly focal character of the lesion We would expect a more diffuse reaction of the reticuloendothelial system to toxins moreover circulating toxins have not yet been demonstrated in tuberculosis (RICH) It would lead us too far afield to discuss the question of the production of tubercles by the release of specific chemical substances when tubercle bacilli disintegrate

The phagocytic and detoxifying functions of the liver are well known and it is easy to believe that this organ is active in rendering harmless both the bacilli and the products of their destruction The presence of such an activity accords well with the histopathological findings for tubercles with caseation are rare in the liver except in miliary tuberculosis — much rarer than in many other sites

In non-caseous tubercles we may expect more variations in structure now that antibiotic and chemotherapeutic treatment is considered of great value in the battle against tuberculosis we try to make use of these variations in estimating the activity of the process Very important are in this respect the presence of epithelioid cells mitoses and polymorphonuclear leucocytes

As we said earlier we imagine that solitary tubercle bacilli are caught within the liver lobule while conglomerates are held up as emboli at the periphery of the lobule it small and within the portal tracts if large Because of the different histological structure of the parenchyma and the portal tract the tubercles formed in them differ Within the lobule there is no connective tissue between the liver cells The reticuloendothelial cells present there chiefly the KUPFFER cells are the principal material for the subtubercles of types III and IV formed there In the portal tracts the cells of the connective tissue also cooperate in the formation of these structures In this way are formed the submiliary tubercles of types O I and II as well as the com-

paratively rare miliary and larger conglomerate tubercles

Not only has the examination of the liver tissue obtained by means of aspiration biopsy and studied in serial section assisted us in localising the different tubercles and establishing their various types, but it has also fortified our belief in the haematogenous dissemination of the process, which is still questioned by some workers We were able to make innumerable observations of subtubercles contiguous to a blood vessel

We believe that the small epithelioid-cell lesions of types III and IV, which are situated in the parenchyma, disappear without leaving a scar It remains an open question whether the reticulo-endothelial cells are resorbed, or whether they revert to the *lining of sinusoids The most probable answer is that both can* occur The portal tubercles, on the other hand, must leave behind them older connective tissue, or scar-tissue, in the shape of hyaline balls, when healing takes place These hyaline balls are seen especially after the healing of caseous tubercles We never directly observed organisation of the caseous centre Penetration of fibroblasts into fibrin was seen several times Serial sections have shown that the periphery of ageing tubercles often consists of a hyaline zone surrounding a centre of epithelioid cells In a few cases we have seen, in a preceding biopsy, exclusively caseous tubercles and hence we presume that in these cases there has been at first a caseous centre afterwards replaced by epithelioid cells In this way the presence of an older hyaline zone surrounding a core of younger tissue becomes understandable Hyperaemic capillaries are sometimes found in the hyaline zone *Serial sections give the impres-*sion that the hyaline substance comes from the blood and that the capillaries represent the pre-existing sinusoids of the liver We find it extremely difficult to decide whether streptomycin may accelerate this scarring process BAGGENSTOSS et al are of the opinion that under the influence of streptomycin young epithelioid-cell tubercles neither caseate nor *encapsulate*

From what precedes it will be clear that generally speaking the age of a disseminated process may be better gleaned from the larger portal tubercles than from the smaller lesions in the parenchyma Generally speaking the latter can only point to a recent dissemination In the acute stage the small epithelioid-cell subtubercles in the parenchyma consist of vesicular cells whose nuclei become pyknotic as they grow older In the beginning a few polymorphs may be present but later only lymphocytes are found Finally it is probable that the entire lesion is resorbed without leaving a scar behind

All this is based on the observations made in the course of serial examinations of positive liver biopsies from 176 patients suffering from tuberculosis Although it is really superfluous we would once again mention the importance already stressed of the examination by serial section of biopsies of a large series of control cases These were provided by some 150 biopsies performed for other indications

Unfortunately we have not yet furnished experimental proof of our views It would at this stage lead us too far afield to discuss the experimental work in progress at the present moment in the attempt to obtain this essential confirmation of our ideas

It is obvious however that we need data on the occurrence of microscopically visible tubercle bacilli in the different foci For this purpose we have preferred the method of HALLBERG (using night-blue) to that of ZIEHL NEELSEN We were especially struck by the fact that acid fast rods were not to be found even in recently caseating tubercles unless a large number of sections were examined We never succeeded in old caseous tubercles In non caseating tubercles we saw acid fast rods only rarely They were never observed in the small epithelioid-cell lesions of types III and IV which however does not mean that they had not been present at an earlier stage of these lesions In all we examined 45 cases using this staining method acid fast rods being found in 15

The results of guinea pig inoculation with a small portion of the liver tissue are in agreement with this In all 70 guinea pig

tests were done, of which only 4 were positive, and this only after on the average four months These observations would support the view that the liver is able to phagocytose and eliminate the tubercle bacilli Experiments have likewise very clearly demonstrated the destructive action of the liver towards tubercle bacilli (LURIE, WESSELS)

In this connection the work of WOODRUFF et al is interesting Tubercle bacilli were cultured from the spleen, the liver and the kidneys of patients who died of pulmonary tuberculosis Often tubercle bacilli were cultured from the liver (especially when there was also abdominal tuberculosis), but better results were obtained from the spleen Positive cultures were obtained most often when caseous tubercles were present According to RICH and FOLLIS tuberculosis of the liver is especially infrequent in cases of pulmonary tuberculosis because of the lowered oxygen tension Experiments on rabbits and guinea-pigs demonstrated this influence of low oxygen tension

It would exceed the scope of this monograph to discuss the problem of immunity against tuberculosis It is reasonable to suppose that factors such as malnutrition, conditioned deficiency, intercurrent infections, pregnancy, lactation, and psychic difficulties may cause a disturbance of the equilibrium between the active disseminating focus and the production of immune bodies That the consequence of this may be overt tuberculosis, in whatever shape is a fact that is confirmed again and again by experience JENSEN's investigations demonstrate very clearly that there are tubercle bacilli of different degrees of virulence It goes without saying that this factor must also play a part in the course of the infection (as JENSEN could prove in his experiments) How far the above-mentioned influences are to be explained immunologically is still an open question We may say that in six cases we observed serious haematogenous tuberculosis after pregnancy This would confirm the old clinical view that the period of lactation is especially perilous in this respect

THERAPY

Finally we will go a little more deeply into the therapeutic consequences of our observations

In the first place it is imperative to realise that an early diagnosis of tuberculosis is of the greatest importance for therapy * One must remember that as a matter of course the greatest therapeutic successes are obtained when the tuberculous process is confined to relatively small lesions no matter which organ of the body is involved, whereas the larger foci hold out less prospect or none at all, of improvement It may therefore be supposed that an effective concentration of anti-tuberculous drugs penetrates into the comparatively small tubercles (types I—IV) we have described, but this happens to a much lesser extent in the presence of caseation, so that the tubercle bacilli then are in a position to multiply

When one keeps this in mind it will be fully realised that the early diagnosis of tuberculosis may be decisive with regard both to the success of therapy and to the ultimate prognosis

As we described in detail above every active tuberculous focus disseminates but this does not necessarily imply that the metastases in their turn will become active foci The possibility exists, however that one or more of them may become the seat of active organic tuberculosis That this possibility is small however, appears from the circumstances that the greater part of the population (viz those who have a positive tuberculin test) may be presumed to have a more or less active focus somewhere in the body, yet they do not develop clinically active tuberculosis It may be presumed that some of us (it is impossible to give an estimate) occasionally pass through an episode of temporary

* Wolf and Florey described in 1945 a young woman who had suffered for six weeks with pyrexia of unknown origin The liver was grossly enlarged An exploratory laparotomy disclosed only large lymph masses in the mesentery Shortly afterwards the patient died and the clinical diagnosis was Hodgkin's disease At autopsy only abdominal tuberculosis with miliary dissemination especially in the liver was found Several weeks later it was reported that tubercle bacilli had been cultured from the blood and urine For us this case would have been an indication for a puncture or liver biopsy (possibly during laparoscopy) as in the case of [illegible] (1946

flaring-up of the process, attended by haematogenous dissemination, without its resulting in overt tuberculosis It is not impossible that this group includes those patients in whom the serial sections of the liver tissue reveal only a few type IV subtubercles The patient overcomes this kind of haematogenous dissemination by virtue of his immunity It would therefore be wrong to treat all such persons with streptomycin, P A S I N H or a combination of these drugs

In which cases, then, must we proceed with specific therapy? It is very difficult to lay down definite rules for all cases The clinical condition of the patient must always be decisive, and the interpretation of clinical symptoms is a very individual matter in doubtful cases In many clinical forms one will have to depend on the result of statistical investigations of the course of the disease

What danger does *premature* administration of antituberculous drugs involve? Those major bugbears of streptomycin treatment, drugresistance and intoxication, are considerably diminished now we have at our disposal several other drugs Nevertheless the development of resistance of the tubercle bacilli to whatever drugs are used remains possible The use of a combination of several drugs has reduced this danger considerably

As a rule we make use of the combination of P A S (P A S-stabilis- for intravenous application) and I N H Streptomycin is reserved for a possible aggravation of the disease or for preparation for operation It is obvious that as one has at one's disposal more potent drugs so one will use them also in the so-called minor forms of tuberculosis (erythema nodosum primary infection etc) Yet nowadays the value of antibiotic and chemotherapeutic therapy in these cases is disputed by many In the second place we must reckon with the risk of intoxication The dosage schemes however are nowadays such that we can neglect this risk in practice

The reader will forgive our inability to give an accurate answer to many of the questions arising in the course of these investigations Most probably he will himself realise that

systematic comparative investigations extending over long periods are required before anyone is in a position to pass a well-founded opinion on the desirability or the necessity of treatment with antituberculous drugs under varying circumstances Aspiration liver biopsy has assisted us in many difficult cases in arriving at a decision whether to apply this therapy or not It goes without saying however that in the majority of cases we allowed ourselves to be guided mainly by the clinical symptoms

What danger does *belated* administration of streptomycin involve? This question also is difficult to answer satisfactorily for the simple reason that use of the term belated may be very elastic An example may make this clear When a patient with serious exudative pleurisy does not respond to conservative therapy, and develops a tuberculous empyema we believe that subsequent drug therapy will be belated This view still too often stubbornly defended that the antituberculous drugs must be reserved until a decided visceral manifestation or tuberculous empyema has developed is wrong for at this stage we can no longer look for quick success with this therapy Some other forms of tuberculosis fall under this heading for instance, in typhobacillosis of Landouzy and in erythema nodosum attended with grave clinical symptoms it is desirable to begin specific drug therapy early

We are perfectly aware that there are all kinds of transitional stages between premature and belated and that there are still many defects in our evaluation of the clinical symptoms with regard to the indication for drug treatment This difficult but rewarding task still lies before the clinician and the pathologist in our opinion the aspiration liver biopsy in an important aid

Conclusion We would like to point out that it has not been our intention to give detailed references to medical literature as that would exceed the scope of this monograph

In placing our experiences of liver biopsy before the reader we have aimed at contributing to a better insight into the

pathogenesis, diagnosis, therapy, and prognosis of haematogenous tuberculosis

We will conclude this monograph by expressing the hope that the day may not be far distant when we shall have at our disposal preparations yet more effective, but less liable to cause complications, than streptomycin, P A S , I N H and similar drugs, and that we soon shall have at our disposal a simple, quick and reliable method for the early diagnosis of tuberculosis, which makes the resource to aspiration liver biopsy superfluous

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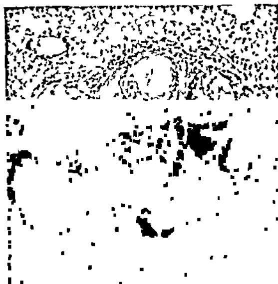
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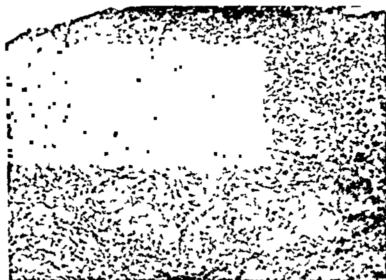
TABLE I

TUBERCLES FOUND IN LIVER BIOPSIES IN CASES OF TUBERCULOSIS

	Frequency of Occurence	Size	Type	Site	Caseation	Giant Cells
Type 0	Extremely rare	Almost a pin's head Average 0.75 mm	Usually a conglomerate tubercle	Portal tract	Possible	Usually present
Type I	Fairly frequent	Minute grayish-white point Average 0.5 mm	Conglomerate or solitary tubercle	Portal tract	Possible	Often present
Type II	Frequent	Very minute grayish white point Average 0.25 mm	Solitary tubercle	Usually portal tract	Possible	Often present
Type III	Very frequent	Grossly invisible Average 0.1 mm	Epithelioid cell subtubercle	Usually parenchyma especially pericentrally	Absent	Exceptional
Type IV	Very frequent	Grossly invisible Average 0.05 mm	Epithelioid cell subtubercle	Parenchyma, especially pericentrally	Absent	Absent



F g 1 A conglomerate tubercle of type O The seven submil arv ep thel o d-cell tuber les so e of the 1 contau ng a g ant cell a e surrounded by hyal ne bands and lymphocytes Haen atoxyl VAN C ESON 100



F g 2 A congl n erate tuber le of type O with central caseation. Ma roscopically this tuber le was the size of a p n s head. × 140



Fig 3 A solitary non-caseating tubercle of type *O* × 100

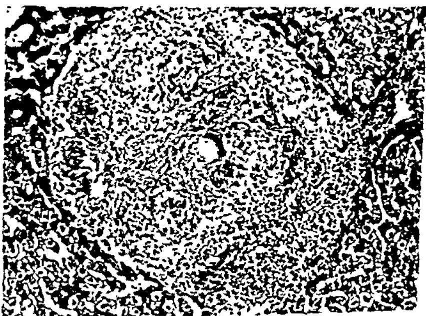


Fig 4 A solitary non-caseating tubercle of type *O* In the middle a giant cell. × 140

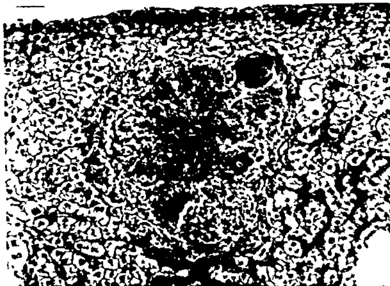


Fig. 5. A young portal epithelioid-cell tubercle of type I. × 160



Fig. 6. A young portal epithelioid-cell tubercle of type I. It shows a giant cell in the middle and at the left hand side a bile duct is seen. × 160

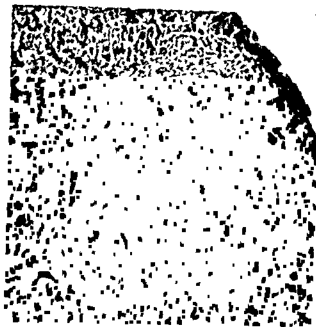


Fig 7 A portal tubercle of type I with central caseation × 140



Fig 8 A portal tubercle of type I with peripheral hyalinization and large-cellular hyperplasia and lymphocytes in the centre In the hyalinizing margin two capillaries are visible × 260



Fig. 9. A portal tubercle of type 1 apparently completely hyalinized. ×60 (see Fig. 10)

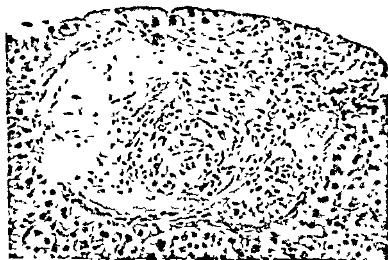


Fig. 10. The same tubercle as in fig. 9, eight sections further. Two [illegible] epithelioid cells have appeared in the centre of the hyalinized connective tissue. ×60

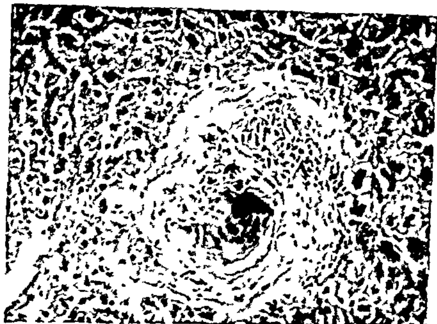


Fig 11 Cicatrization of a portal tubercle of type I with a giant cell × 280

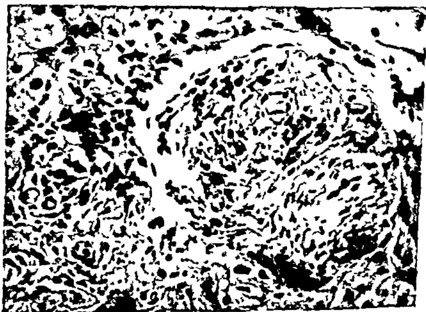


Fig 12 The scar of a portal tubercle of type I × 280

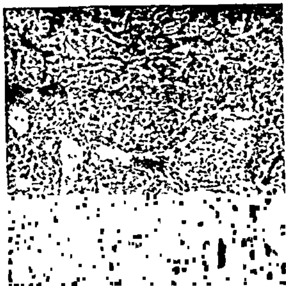


Fig. 13. A portal tubercle of type II abutting on an interlobular vein. × 140 (see fig. 14)

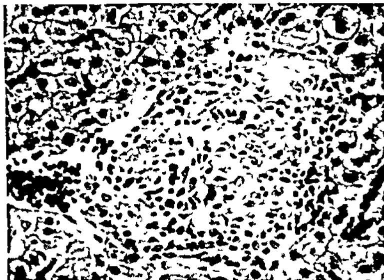


Fig. 14. The same tubercle as in fig. 13 at higher magnification. Large-cell hyperplasia. × 400



Fig 15 A subacute portal tubercle of type II × 240

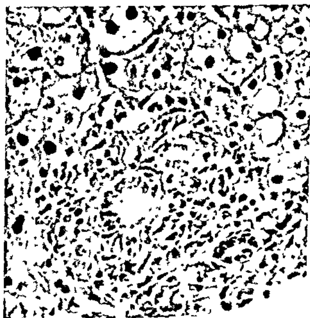
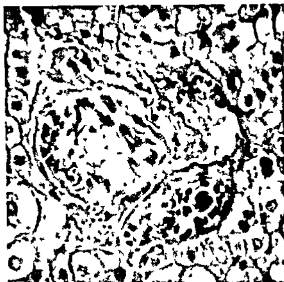


Fig 16 A later portal tubercle of type II The nuclei of the fibrocytes are long and thin To the right hand side below a bile duct is seen × 400



F g The scat f a portal tube le f t pe ll 400

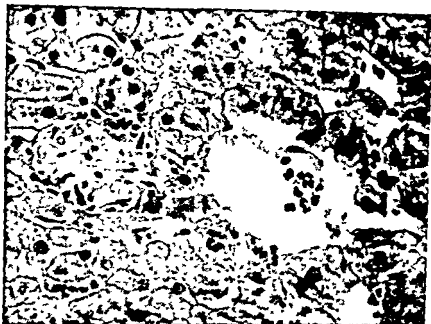


Fig 18 An epithelioid-cell subtubercle of type III in the neighbourhood of a central vein × 400 (see fig 19)



Fig 19 The same lesion as in fig 18 × 800

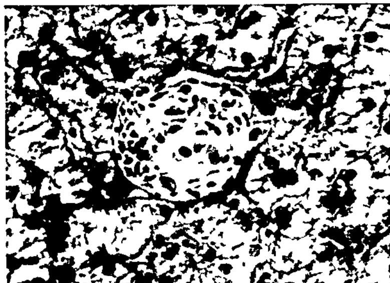
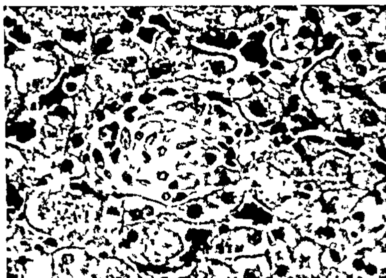
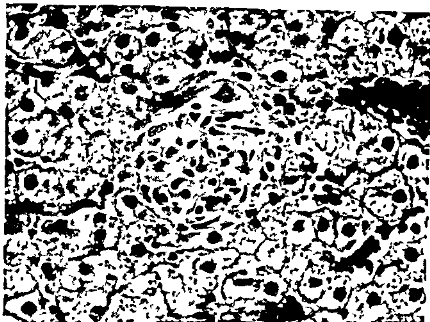


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F g 22 A later epithel oid-cell subtubercle of type III vaguely delimited from the surround ng parenchyma 560

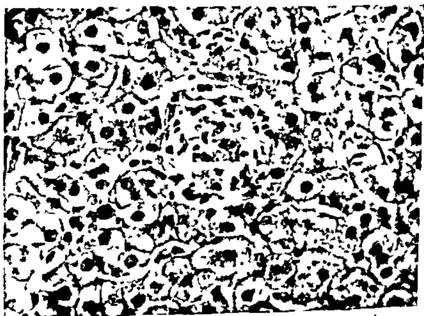
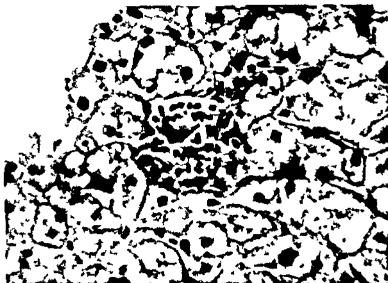
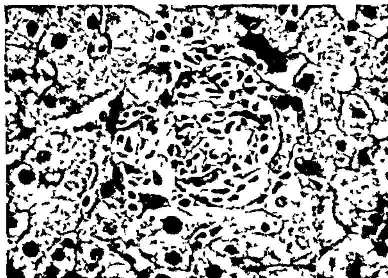


Fig 23 A more advanced epithel oid-cell subtubercle of type III almost hidden in the paren chyma × 560



I g 24 An old ep helund-cell subtuber le f type III < o



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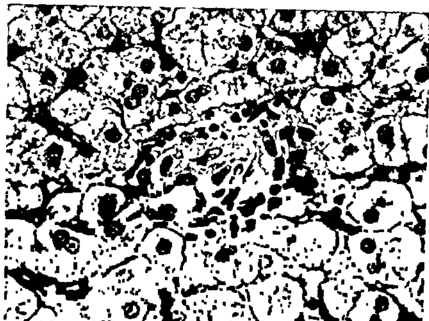


Fig 26 A young epithelioid-cell subtubercle of type IV × 560

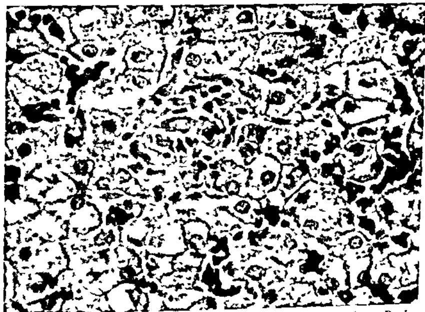


Fig 27 A young epithelioid-cell subtubercle of type IV hidden in the parenchyma Besides lymphocytes a polymorphonuclear leucocyte is visible × 560

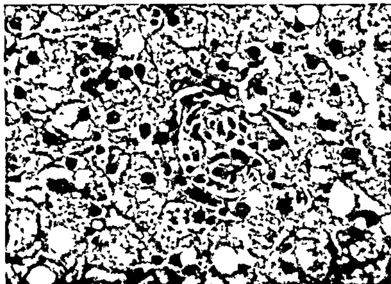


Fig. 28. An older epithelioid-cell subtubercle of type IV containing numerous lymphocytes and also one polymorphonuclear leucocyte. ×560

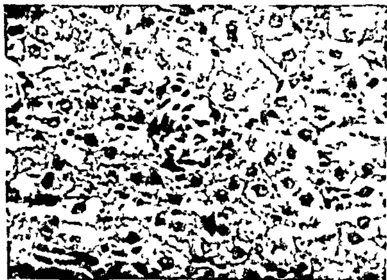


Fig. [illegible]. An old epithelioid-cell subtubercle of type IV. [illegible]

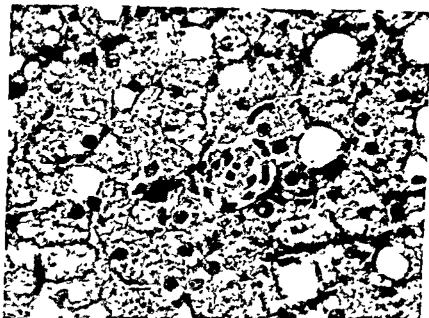


Fig 30 A rather young minute epithelioid-cell subtubercle 560

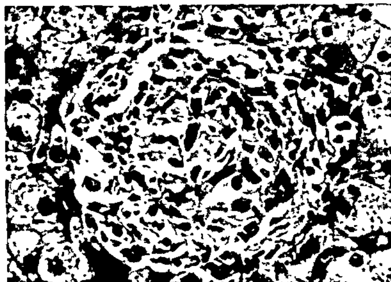
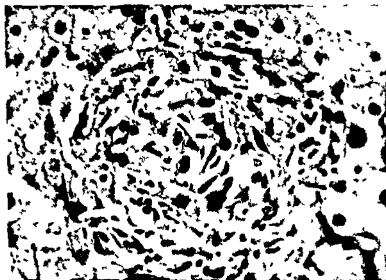


Fig. 31. A young epithelioid-cell tubercle with a mitosis. × 560 (see fig. 32)



The same tubercle … one section further. Here another segment of the same mitosis is seen. × … (see fig. 31)

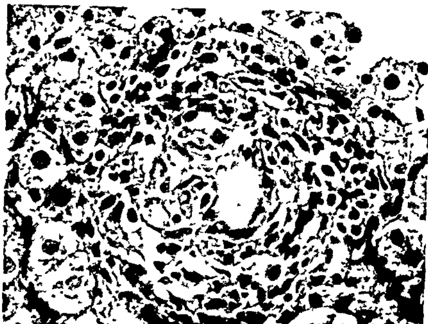


Fig 33 The same tubercle again one section further Besides a giant cell part of a second mitosis has appeared 560 (see fig 34)

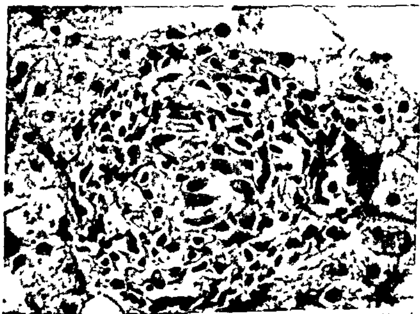


Fig 34 The same tubercle again one section further The giant cell is still partly visible and another segment of the mitosis from fig 33 is seen 560

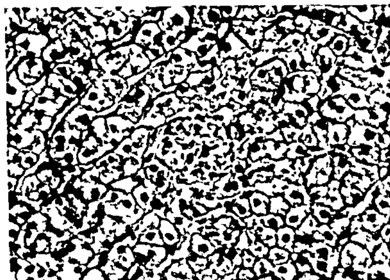


Fig. 11. A tiny, barely visible young epithel[illegible]d-cell subtubercle with a cluster m[illegible]. 400

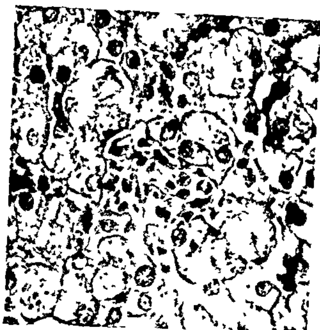


Fig 36 A developing epithelioid-cell subtubercle with a diaster mitosis. × 640

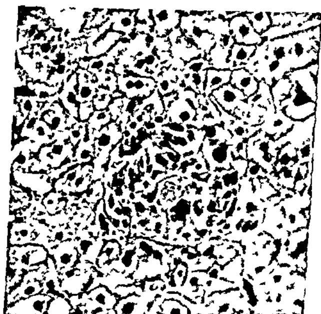


Fig 37 An aspiration liver biopsy of a patient with pulmonary tuberculosis and anthracosis The protoplasm of the KUPFFER cells forming this type III lesion (situated in the neighbourhood of the central vein) is loaded with coal dust particles × 400



Fig. [illegible] The liver of a patient who died of hyperacute tuberculous infection. A phagocytosed acid-fast rod is seen in the cytoplasm of a Kupffer cell (Ziehl-Neelsen stain). Immersion enlargement.

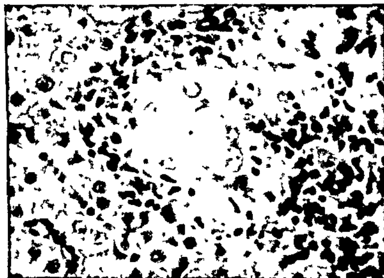


Fig. [illegible] An asteroid body in a giant cell in a liver tubercle. The patient suffers from Addison's disease due to tuberculosis. These inclusions are not pathognomonic of Boeck's sarcoidosis. × [illegible]